ANONYMOUS AND PUNITIVE: MUTUAL AID ADDICTION THERAPIES IN MEXICO CITY

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Over the past decade, Mexico has seen a disturbing increase in violence related to the War on Drugs as well as an increase in the problematic use of addictive drugs, particularly crack cocaine. Meanwhile, it is estimated that over 90% of Mexico's addiction treatment is provided by Alcoholics Anonymous-based residential treatment centers, invented in Mexico, referred to as *anexos*—the vast majority of which are not regulated by the State.

In 2012-13, I conducted 5 months of ethnographic fieldwork in the metropolitan area of Mexico City with a focus on 3 different anexos. Regular observations were made of the treatments provided, and interviews were done with patients and *padrinos* (recovered addicts who ran the anexos). This form of mutual aid care was found to employ rehabilitation techniques that go far beyond the typical 12-step paradigm and include isolation and shackling; physical beatings and *aplicaciones* (sustained, painful body postures); and religious indoctrination. Nevertheless, families seeking care for relatives frequently resort to the anexos as the only form of addiction care they can afford or are aware of, with many families assisting the anexos to admit and retain the relative against his/her will for months at a time.

In the setting of minimal resources and high levels of violence and stigma related to substance use, new forms of mutual-aid residential treatment are developing in Mexico City. These groups employ therapeutic interventions that challenge assumptions about the lines between therapy and abuse, and between patient autonomy and family safety. Now that Mexican authorities are attempting to regulate these treatment centers (with funding from the US government), with an emphasis human rights, this scenario presents a unique challenge to the development of a nation-wide public mental health system. This effort will be aided and further studied with additional fieldwork in 2013 and 2014.

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MACROPHAGE POLARIZATION IN RESPONSE TO WEAR PARTICLES IN VITRO

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Total joint replacement is a highly successful surgical procedure for treatment of patients with disabling arthritis and joint dysfunction. However, over time, with high levels of activity and usage of the joint, implant wear particles are generated from the articulating surfaces. These wear particles can lead to activation of an inflammatory reaction, and subsequent bone resorption around the implant (periprosthetic osteolysis). Cells of the monocyte/macrophage lineage orchestrate this chronic inflammatory response, which is dominated by a pro-inflammatory (M1) macrophage phenotype rather than an anti-inflammatory pro-tissue healing (M2) macrophage phenotype.

While it has been shown that interleukin-4 (IL-4) selectively polarizes macrophages towards an M2 anti-inflammatory phenotype which promotes bone healing, rather than inflammation, little is known about the time course in which this occurs or conditions in which repolarization through IL-4 is most effective. The goal of this work was to study the time course of murine macrophage polarization and cytokine release in response to challenge with combinations of polymethyl methacrylate (PMMA) particles, lipopolysaccharide (LPS), and IL-4 in vitro.

Treatment of particle-challenged monocyte/macrophages with IL-4 led to an initial suppression of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) production and subsequent polarization into an M2 anti-inflammatory phenotype. This result was optimized when IL-4 was delivered before PMMA particle challenge, to an M1 phenotype rather than to uncommitted (M0) macrophages. The effects of this polarization were sustained over a 5-day time course. Polarization of M1 macrophages into an M2 phenotype may be a strategy to mitigate wear particle associated periprosthetic osteolysis.

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PREVALENCE OF ANAL DYSPLASIA AND HPV IN INFLAMMATORY BOWEL DISEASE PATIENTS

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The incidence and prevalence of anal dysplasia and anal cancer is higher in immunosuppressed patients (HIV and solid organ transplant patients) compared to non-immunosuppressed patients. We studied the risk of anal dysplasia and cancer in patients with inflammatory bowel disease (IBD) who are on chronic immunosuppressive therapy and in patients who are not on immunosuppressive therapy to determine if immunosuppressed IBD patients are at increased risk of anal dysplasia.

Patients with IBD (Crohn's disease or ulcerative colitis) were recruited to participate in the study. Participants completed an anonymous self-administered questionnaire to assess risk factors for HPV and anal cancer. Medication history and duration of immunosuppression were recorded. Anal Pap smear was performed to obtain a sample of cells for anal cytology and HPV testing.

192 patients with IBD were included in our study. 102 IBD patients were on immunosuppressive therapy and 90 IBD patients were on non-immunosuppressive therapy. The prevalence of abnormal anal Pap smears was 9.8 % in immunosuppressed patients and 4.4% in non-immunosuppressed patients. Immunosuppressed patients were 2.34 times more likely to have abnormal anal Pap smears when compared to IBD patients on non-immunosupressive therapy (95% CI = 0.71 – 7.73, p= 0.154).

Our study revealed an association between chronic immunosuppression and anal dysplasia. IBD patients on immunosuppressants have a higher prevalence of anal dysplasia compared to those not on immunosuppressants. Only 14.2% of patients with abnormal anal Pap smear results were HPV positive, challenging our hypothesis that HPV (16,18) positivity correlates with anal dysplasia. We continue to recruit age-matched healthy controls to better understand the risks of anal cancer in IBD patients when compared to healthy controls.

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MEASURING PHYSICIAN GROUP CONSOLIDATION AND ITS EFFECTS ON PRICE BARGAINING

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Consolidation within the health care system has arisen as providers and insurers attempt to improve quality of care, enhance efficiency, and lower costs. Recent legislative actions enable the formation of accountable care organizations (ACOs), which are expected to promote further consolidation of hospital systems and physician groups. But an increased market share could also reduce competition and provide larger groups with stronger positions in negotiating more favorable (higher) prices with insurance companies.

While studies have been able to investigate the effects of merging in hospital and insurance markets, there has been little done to examine physician practice consolidation. It is well known that the composition of physician groups has been affected by the emergence of the managed care system. For example, there has been a significant increase in the percentage of surgical and medical specialists who are part of larger physician groups instead of solo or two-person practices. One potential reason for the dearth in studies examining physician group changes is the challenges presented in efficiently and accurately evaluating the size and concentration of physician practices within the United States.

The primary goal of this study was to examine the relationship between physician practice size and payments for services covered by private insurance companies. Our methodology relies upon data collected by private insurance and Medicare claims databases. We present a novel methodology for measuring groups' relative market concentration within discrete geographical regions. Next, we evaluate and identified the highest volume procedures conducted by specialty at the national level. Finally, we examined how prices for these procedures vary between areas of differing competitiveness. Our preliminary data suggest that physician groups' pricing for high volume procedures are highly correlated to the competitiveness in a given region. The study helps in assessing the cost and benefits of physician practice consolidation and provides insight into future policy decisions that may influence physician group concentration in the United States.

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PROFILING RISK FACTORS FOR UVEITIS IN JUVENILE ARTHRITIS: A NEW MODEL FOR EHR-BASED RESEARCH

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Chronic uveitis is a common and serious co-morbid condition of JIA with insidious presentation and potential to cause blindness. Knowledge of clinical associations will improve risk stratification. Based on clinical observation, we hypothesized that allergic conditions are associated with chronic uveitis in JIA patients.

To analyze patient characteristics associated with chronic uveitis in a large JIA cohort using a novel text-mining approach to analyze retrospective EHR data.

Retrospective cohort study using Stanford's clinical data warehouse. Clinical notes (2000-2011) were processed via a text analytics pipeline. Univariate-associated variables were used in a multivariate logistic regression adjusted for age, gender, and race. Previously reported associations were evaluated to validate our methods.

Previously reported associations with uveitis in JIA patients (earlier age at arthritis diagnosis, oligoarticular-onset disease, ANA status, history of psoriasis) were reproduced in our study. Use of allergy medications and terms describing allergic conditions were independently associated with chronic uveitis. The association with allergy drugs when adjusted for known associations remained significant (OR = 2.54, 95% CI 1.22-5.4).

This study shows the potential of using text-analytics on clinical data warehouses to examine practice-based evidence for evaluating hypotheses formed during patient care. Our study reproduces four known associations, and reports a possible association between allergic conditions and chronic uveitis in JIA patients. Once confirmed in prospective studies, it may inform pathogenic mechanisms, alter treatment strategies, and guide uveitis screening in patients with allergic conditions.

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AN INVESTIGATIONAL STUDY TO EVALUATE SILDENAFIL FOR THE TREATMENT OF LYMPHATIC MALFORMATIONS

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Lymphatic malformations (LMs) are localized areas of abnormal development of the lymphatic system. Patients may present with pain, secondary infection, complications due to specific organ involvement, and death. Recently, we reported marked regression of LMs in three children after treatment with oral sildenafil (Swetman et al, NEJM, 2012). The objective of this investigational open-label study was to assess the efficacy of 20-weeks of oral sildenafil in reducing the volume and symptoms of children with LMs.

Dosing for sildenafil was based on the European Medicines Agency guidelines as follows: if the subject weighed more than 20 kg, 20 mg was given three times a day (60 mg/day); if the subject weighed between 8 kg and 20 kg, 10 mg was given three times a day (30 mg/day). LM volume was calculated blindly using magnetic resonance imaging (MRI) that was performed before and after 20 weeks of sildenafil. Clinical response was assessed on weeks 0, 4, 12, and 20 and both the physician and parent evaluated the LM in comparison to baseline. Seven children (N=7; 4 boys, 3 girls; ages 13-79 months) with LMs enrolled and completed 20 weeks of sildenafil. LM locations included head/neck (N=6) and abdomen (N=1). Four subjects had a LM volume decrease (1.0-31.70%). Two subjects with a LM volume increase (1.1-3.7%) experienced clinical improvement including improvement in sleep apnea scores. One subject had a 29.6% increase in LM volume and had no therapeutic response. The LMs of all six subjects who had experienced a therapeutic response on sildenafil softened and became easily compressible. Adverse events while on sildenafil were minimal. Several subjects requested to continue sildenafil after study completion because of the improvement they perceived.

Sildenafil can be effective in reducing the volume and symptoms in some children with LMs. A larger, randomized controlled trial will be necessary to verify the beneficial effects of sildenafil on LMs, as well as to determine which types of lesions respond best.

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SUN PROTECTIVE BEHAVIORS & BELIEFS AMONG RUNNERS

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To assess the sun protective behaviors and beliefs in a defined population of recreational and competitive runners who would be expected to have increased sun exposure due to participation in their sport. A cross-sectional study was conducted using an online survey administered to 697 runners.

Of the seven sun protective behaviors asked about, the majority of runners report moderate utilization of five and frequent utilization of two, which was more frequent than the general United States population. 72.0% of runners who did not use sunscreen regularly cited reasons that included forgetfulness (48.0%), discomfort (17.4%), inconvenience or laziness (4.1%); only 9.3% cited the use of another sun protective behavior. 57.3% of all runners reported that their sun exposure habits were primarily influenced by reasons related to their skin health including fear of skin cancer (39.0%), fear of skin aging (16.0%) and to avoid sunburn (2.2%). Another 5.5% cited optimizing vitamin D (4.2%). 32.9% of respondents said that practical reasons or a lack of interest influenced their sun exposure habits most, and the primary influence for 3.0% was to maintain a tan.

The majority of the runners studied did not consistently utilize some form of sun protective behavior despite 55% of runners citing either a fear of skin cancer or skin aging as the primary influence of their sun exposure habits; comfort, convenience and forgetfulness appear to be most influential. Continuing efforts to educate runners of adverse health consequences of sun exposure is important. Interventions that address issues of convenience and forgetfulness may help modify sun exposure behaviors in this population.

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RELAXIN AS A POTENTIAL HORMONAL RISK FACTOR FOR FEMALE ACL INJURY

Malcolm DeBaun and Jason Dragoo, Department of Orthopaedic Surgury

Relaxin is a peptide belonging to the insulin family of hormones that has been shown to play an active role in the remodeling of collagen through the upregulation of collagenases, metalloproteases, and tissue plasminogen activator. This hormone has been associated with ligamentous remodeling in mammals to allow parturition, and may predispose female athletes to a higher risk for anterior cruciate ligament (ACL) injury.

Our most recent published study of 128 participants demonstrated the mean serum relaxin level for female athletes with ACL tears was significantly higher than those women without ACL tears. Additionally, relaxin receptors were identified in female ACL tissue, but not in males. Injection of relaxin has also been associated with decreased ACL strength in animal models. This data suggests relaxin may play a role in altering the collagen structure and integrity of the female ACL.

We are currently recruiting participants to analyze the levels of relaxin within their knee joint cavity. We hypothesize that athletes with higher levels of serum relaxin will have corresponding increased levels of synovial relaxin within their knee. In the future we will evaluate relaxin ability to induce a signal within tenocytes harvested from female ACL tissue by analyzing levels of cAMP.

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ONE TWO TRIAGE: A NOVEL TRIAGE SYSTEM

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Emergency medicine depends on time-sensitive intervention to prevent avoidable death or disability from injuries and illnesses. Increasingly busy Emergency Departments need a systematic approach to prioritizing the care of patients depending on the severity of their illnesses /injuries. Most high-income countries have developed triage scales to accomplish this task. However these scales often require experienced providers (e.g. Emergency Severity Index [ESI]) or the requirement for specialized resources, such as computerized algorithms (e.g. Manchester Triage Scale). In lower-income countries neither experienced providers nor computer resources may be available. We sought: (1) to evaluate validity by comparing OTT to a gold standard of physician-determined acuity level of patient illness; (2) to compare the OTT scale to an existing, previously validated scale used commonly in United States Emergency Departments, the ESI. We calculated unweighted kappas (denoted by $\kappa\kappa$, quadratic weighted κ , expert-defined weighted $\kappa\kappa$and triage-weighted κ in order to assess agreement between OTT and ESI groups with the gold standard.

482 triply-blind triages were completed by Stanford undergraduates employing OTT, nurses employing ESI, and physicians directly assessing severity. Using the quadratic weighted κ, agreement with the gold standard was moderate for both OTT (κ=0.46 95% CI [0.37, 0.55]) and ESI (κ=0.57 95% CI [0.43, 0.66]. Agreement with the gold standard improved to (κ= 0.64 95% CI [0.54, 0.74] for OTT and κ= 0.65 95% CI [0.56, 0.75] for ESI) after prevalence of acuity levels defined by the gold standard was normalized to 100 patients per level. Using the expert-defined weighted $\kappa\kappa\kappa$ the agreement was moderate for both OTT and ESI (κ=0.48 95% CI [(0.43, 0.53] and$\kappa\kappa$=0.49 95% CI [0.44, 0.55], respectively). Agreement with gold standard increased for OTT (0.50 95% CI [0.43, 0.57]) and decreased for ESI (0.34 95% CI [0.27, 0.40]) after balancing the prevalence across triage levels.

When compared with the gold standard of physician triage, the validated system ESI and the novel system OTT performed similarly. Under standard quadratic weighting for κ, ESI and OTT overlapped significantly at the 95% confidence level, suggesting both triage methods perform similarly. The agreement improved after scaling observations to 100 patients at each triage level by the gold standard. OTT out-performed ESI when under-triaging by the test system vs. the gold standard was treated more severely than over-triaging, by means of a kappa with expert-determined asymmetric weightings.

PEDIATRIC DERMATOLOGY IN CALIFORNIA: AN ASSESSMENT OF NEED AND ACCESS

Alexander L. Fogel, Joyce Teng MD, PhD.Department of Dermatology

Pediatric patients are estimated to comprise 58% of all patients seen in general dermatological practices, and many pediatric skin diseases are treated by non-dermatologists. This situation is undesirable, as research suggests that pediatric dermatologists are less likely to misdiagnose and/or improperly treat pediatric skin diseases. While research indicates that children are underserved with regard to dermatological care, the state of pediatric dermatology in California has not been assessed. This project seeks to analyze the state-wide distribution of pediatric dermatologists with the goal of assessing patient needs and access to care.

A comprehensive database of board-certified pediatric dermatologists in California was assembled through an analysis of board-certification records, state-wide certification listings, medical society memberships, and university affiliations. It was determined that 57 providers currently practice in California, and 35% (20/57) practice in a university setting. Though 82% (47/57) of providers are concentrated in the Greater Bay Area, Los Angeles Area, and San Diego Area, these regions are home to only 47% of California's children. At the county level, provider distribution ranges from 0 – 7.17 per 100,000 children, and 74% (43/58) of counties have zero providers. 48% of California's children live in a county with one or zero providers. In addition, an inverse relationship was found between the number of providers per 100,000 children and the county pediatric population.

These findings suggest that access to pediatric dermatological care is severely limited in most areas of California, particularly in rural areas. This is driven by the concentration of providers in urban areas, and this pattern may be related to the large fraction of physicians practicing at universities medical centers. Future research will assess the distribution of providers nationwide, develop metrics of access through surveys of physicians and patients, and produce recommendations to efficiently manage the shortage of pediatric dermatological care through telemedicine models.

IMMUNIZATION COVERAGE AMONT JUVENILE JUSTICE DETAINEES IN A NORTHERN CALIFORNIA DETENTION FACILITY

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Adolescents in the U.S. continue to lag well behind immunization coverage goals. A combination of age, risky health-related behaviors, poor healthcare access and congregate living in detention contribute to the increased vulnerability of adolescents involved with the juvenile justice system to vaccine-preventable diseases. Currently, though, few data exist about immunization coverage levels among detained adolescents and none examine recent additions to the Advisory Committee on Immunization Practices (ACIP) recommendations like HPV and meningococcal vaccines. The principal aims of this study were to quantify the baseline immunization coverage of adolescents entering a juvenile justice system, and assess the effect of detention-based clinical care on immunization coverage in youth.

A cross-sectional retrospective review was performed of a systematic sample of medical records of 279 adolescents aged 10-19 years detained at a large, Northern California juvenile detention facility. The immunizations studied include: tetanus, diphtheria and acellular pertussis (TdaP), quadrivalent meningococcal vaccine (MCV4), hepatitis A (HepA; 2-shot series), varicella-zoster-virus (VZV; 2-shot series), and HPV (Gardasil; 3-shot series). Only 3% of detained adolescents had received all nine study immunizations prior to their first detention at the juvenile facility. Prior to first detention, immunization coverage for detained youth was significantly lower than average coverage rates for the general adolescent population in California for all vaccines ($p<0.01$) except for the first doses of hepatitis A and varicella zoster virus vaccines. However, most individual immunization coverage levels increased and were significantly higher than the general adolescent population at the most recent detention.

Significantly lower levels of vaccination coverage exist among justice-involved youth prior to their entry into the juvenile justice system than the already under-vaccinated general adolescent population. Especially low levels were found for the newer vaccines, which have not been mandated by school-entry laws (i.e. MCV4 and HPV among girls and boys). Increased immunization coverage was found among adolescents after detention. An institutional commitment to routine administration of recommended adolescent and catch-up vaccinations to detained youth represents a sound public health approach and can enable detained youth to achieve levels of immunization coverage equivalent to the general adolescent population.

INTENSITY MODULATED RADIATION THERAPY RESULTS IN SIMILAR SURVIVAL TO 3D-CONFORMAL RADIATION FOR STAGE III NON-SMALL-CELL LUNG CANCER

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For stage III non-small-cell lung cancer (NSCLC) the most commonly used radiation technique is 3-dimensional conformal radiation therapy (3D-CRT), although intensity modulated radiation therapy (IMRT) is being increasingly employed. There are concerns that breathing-associated tumor motion may decrease the radiation dose to portions of a tumor when using IMRT, which could potentially lead to inferior clinical outcomes. No randomized studies have compared these treatments. Thus, we performed a population-based comparative effectiveness analysis of radiation treatment strategies for stage III NSCLC.

We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data to identify 5,846 patients aged 65 or older with stage III NSCLC from 2002-2007, whose treatment included radiotherapy. Using Cox regression and propensity score matching, we compared IMRT, 3D-CRT, and the older method of 2D based planning and simulation (2D-RT) with regards to overall and cancer specific survival (OS, CSS). IMRT was associated with similar OS (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.85-1.09) and CSS (HR 0.92, 95% CI 0.80-1.06) compared to 3D-CRT. Statistically significant superior OS and CSS were associated with IMRT and 3D-CRT compared to propensity score matched 2D-RT cohorts.

A randomized trial of radiation techniques for advanced stage NSCLC is highly unlikely. Previous studies have focused on single institutional experiences, and by turning to population-based data we have accumulated the largest patient cohorts of these techniques. We found that for stage III NSCLC, IMRT results in similar OS and CSS to 3D-CRT, and both are superior to 2D-RT.

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LATE REFERAL TO PALLIATIVE CARE CONSULSTATION SERVICE: LENGTH OF STAY AND IN-HOSPITAL MORTALITY OUTCOMES.

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Departments: Internal Medicine

Palliative care services in the United States are increasing in their prevalence but continue to vary in their implementation, with different approaches to palliative care team composition, referral policies and patient access to services. Stanford Hospital's Palliative Care Service currently depends on referrals from inpatient attending physicians, with no current policies or triggers guiding when patients are referred to palliative care. As a result, there is potential for large variability in the time similar patients may wait before being referred to palliative care. For patients who receive a palliative care consult, it is important to understand whether the timing of referrals has an impact on patient outcomes, as this can help optimize care and guide hospital policies. While some studies have found lower quality of care associated with later referrals to hospice, it is currently unknown what impact the timing of inpatient palliative care consultation has on patient outcomes.

The objective of this study is to better understand the impact that referring earlier vs. later to palliative care has on patient outcomes including length-of-stay, in-hospital mortality and patients' desire to limit aggressive interventions.

A retrospective analysis was done on patients with pre-existing oncologic diagnoses who received a palliative care consultation (n=1249) since the establishment of Stanford Hospital's Palliative Care Service. Multiple linear & logistic regression analyses were applied to data to look at the impact of timing of referral on patient outcomes.

Those oncologic patients referred to palliative care in the first week following admission had shorter lengths of stay, a greater desire to limit aggressive interventions and lower in-hospital mortality as compared to patients referred after one week. Groups were similar in terms of DNR status, level of sickness as measured by number of recent inpatient admissions, and demographic variables, except later referrals tended to be younger and were more likely to be white. Groups differed significantly in time-to-consultation and length-of-stay following consultation. Regression analyses, adjusted for demographic variables, DNR status and sickness revealed that for each day palliative care consultation was delayed, length-of-stay following the consult was associated with an increase of 0.22 days ($P<0.001$). Waiting one week or more to refer a patient was associated with an overall increased length-of-stay of 2.76 days ($P<0.001$), which increased to 5.27 days ($P<0.001$) when patients who died in-hospital were removed from the data, suggesting in-hospital mortality was not independently driving the trend. Waiting one week or more to refer was associated with increased odds of a patient dying in the hospital (vs. being discharged alive) by a factor of 3.15 ($P<0.001$). Additionally, if a patient was referred in the first week, the odds of the patient deciding to limit aggressive interventions increased significantly (OR:1.7; $P<0.001$).

Recent studies have shown that decreased hospital length-of-stay for advanced cancer patients has been linked to increased patient quality of life, decreased hospital-acquired infection rates and decreased patient and hospital cost. If palliative care referral timing has the capacity to impact length-of-stay, and allow for potentially improved care and patient quality of life at lower cost, this argues for the design and implementation of hospital policies that encourage early referral to palliative care for advanced cancer patients.

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MECHANISM OF INTERACTION BETWEEN REGULATORY T CELLS AND DENDRITIC CELLS IN HUMAN ALLERGIC ASTHMA

Sohan Japa and Kari Nadeau. Department of Pediatrics, Division of Allergy and Clinical Immunology

Asthma is an inflammatory process affecting the bronchial airways that is marked by eosinophilic inflammation, mucus hypersecretion, and bronchial hyperreactivity. Dendritic cells and regulatory T cells have been implicated in the underlying pathogenetic mechanism of the disease. Traditional paradigms have focused on the role of helper type 2 T cells. However, new studies have shown the importance of dendritic cells in the pathogenesis of the disease. A complex, two-way communication between dendritic cells (DC) and regulatory T cells (Treg) is believed to mediate the balance between immunogenicity and tolerance. More specifically we hypothesize that the ratio of mDCs/pDCs will be different in healthy controls versus atopic asthmatics. We believe that pDCs and immature dendritic cells are able to take up antigen and cause anergy in T cells and promote regulatory T cells, which suppress the functions of effector T cells. In contrast, mature dendritic cells and possibly mDCs may promote the growth of effector T cells.

In the first phase of the project, we attempted to isolate DC subsets and perfect our DC isolation method. This proved to be very difficult and took up most of the research time. DC are extremely rare and their enrichment was difficult. We first attempted DC isolation only using FACs (markers were Lin 1, HLA-DR, CD123, and CD11c), but since that produced DC populations <1%, we sought out other methods. Very few labs in the country were doing such work, which made it difficult to find advice/help in this area. We then attempted to use commercial kits that employ other enrichment approaches (e.g., magnetic beads) prior to using FACs. This two step approach improved yields but only marginally. Nonetheless, there was enough to start doing some preliminary analysis. We first compared mDC populations with pDC populations in healthy controls and atopic asthmatics. However, the mDC/pDC ratio did not differ significantly in the two groups, disproving our hypothesis. This initial data may suggest that mDC/pDC ratio is not a significant factor in dictating tolerance versus immunogenicity in asthma. Nonetheless, overall maturity of DCs may still explain the variance in immunological states.

As outlined above, the project overall proved to be very challenging and though I did not complete all of the original aims, I learned a lot in the process. First, the legwork for the project forced me to understand the interactions between Tregs and DCs at a very fundamental level which required reading not only the latest papers but as well as textbooks on immunology. Second, I gained many skills in the lab. Since it was my first time in a wet lab, I picked up on basic techniques such as handling and storing cells, and proper pipetting. I also gained mastery of using the FACs machine to isolate cell lines. Lastly, the nature of the project forced me to seek constant help from people outside the lab. In hindsight, I think the project may have been overly ambitious for the time period I was seeking to conduct the research in. Nonetheless, I think it was a great experience overall.

Future work should include optimizing the DC isolation method and further subtyping DCs into immature, semi-mature, and mature types. The results of the study will confirm and expand on current theories regarding dendritic cell and Treg interaction and potentially pave the way for novel therapeutic modalities to treat asthma.

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DIAGNOSTIC DISCREPANCIES BETWEEN SECOND-OPINION AND REFERRING PATHOLOGY REPORTS OF NEUROENDOCRINE TUMORS

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The nomenclature and histologic classification schemes for neuroendocrine tumors (NETs) have historically been heterogeneous and inconsistent. However, clinicians require specific descriptors to determine treatment plans for patients. In 2010, Klimstra, *et al.* published a set of NET pathology reporting guidelines. Using these guidelines, we undertook a systematic evaluation of discrepancies between referring versus Stanford second-opinion NET pathology reports. We developed a cohort of all NET cases seen at Stanford University Hospital between April 1998 and December 2012 with available Stanford and referring pathology reports for the same specimen to identify the discrepancies between their clinical diagnoses.

Of 170 cases, histological diagnoses were discrepant in 79% of the reports; 89 (66%) of which were clinically insignificant, and 46 (34%) clinically significant. Stanford used 14 unique terms for histological description, and referring institutions used 49 unique terms. Grade, mitotic index (MI), and Ki67 were among the variables examined; they were not reported (NR) from the majority of cases in one or both reports, yet more likely to be included in the Stanford report. Grade was NR in one or both reports in 152 cases (89%); of the 18 cases reporting grade in both reports, 3 (2%) were discrepant. MI was NR in one or both reports in 128 cases (75%); of the 42 cases reporting MI in both reports, 27 (16%) were discrepant. Ki67 was NR in one or both reports in 153 cases (90%); of the 17 cases reporting Ki67 in both reports, 12 (7%) were discrepant. Reporting was found to improve over time for these variables (five-year blocks from 1998-2012). There was a trend towards improved reporting from academic hospitals (vs. non-academic hospitals) and by Stanford NET pathology experts (vs. general pathologists).

Clinically relevant differences were frequently found between Stanford and referring pathology reports for NETs. Future studies of NET pathology discrepancies are warranted to allow additional time for adoption of the 2010 guidelines.

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THIS MEDICAL STUDENT LIFE: USING PODCAST STORYTELLING TO PROMOTE REFLECTIVE PRACTICE IN CLINICAL STUDENTS.

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The clinical years are widely recognized to be a time of profound growth and also distress. Medical students begin to identify as physicians, but they also experience a decrease in mental wellbeing, empathy, and professionalism. Numerous studies have examined narrative medicine techniques which employ reflective writing to combat this process of "ethical erosion." However, researchers have noted that students often do not make time for these practices within the constraints of their demanding and inflexible schedules. Relatively little work has been done on "digital storytelling," the use of multimedia to promote reflection, and no work within this field has specifically examined medical student oral storytelling.

We crafted a series of podcasts featuring interviews with clinical students at Stanford and examining themes relevant to the clerkship years. We were impressed by the range, depth, and emotional power of the storytellers, most of whom were not trained in the performing arts. Original podcasts can be streamed at our website:

www.thismedicalstudentlife.org

Early qualitative feedback suggests that telling a story for this project prompts students to reflect critically on their experiences in medical school. Future research could expand on these findings by designing and piloting a professionalism and wellness curriculum utilizing digital oral storytelling.

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DEVELOPMENT OF TUBERCULOSIS LABORATORIES IN CHINA

Anna Luan and Niaz Banaei. *Stanford School of Medicine, Stanford Department of Pathology, Stanford Department of Infectious Diseases.*

Tuberculosis (TB) is an airborne infectious disease that is preventable and curable, but is second only to HIV/AIDS as the greatest killer worldwide from a single infectious agent. Untreated TB kills half of its victims, mostly in low- and middle-income countries, and each case causes 10-20 more. The WHO estimates an incidence rate of more than 1.3 million new cases of TB each year in China, of which 120,000 cases are from multidrug resistant (MDR) strains. Appropriate laboratory testing, including adequate training of personnel and quality assurance, is crucial in treating TB early and correctly. Errors in specimen processing, culture, and microscopy are likely to lead to misdiagnosis, therefore compromising efforts to control TB in China. Many laboratories are staffed inadequately, and training across facilities in inconsistent. Thus, the long-term goal of this project is to support the Shanghai CDC in their efforts to develop national guidelines and methods of quality assurance, and provide testing of individuals known or suspected of having drug resistant TB. Specifically, this project aims to assess the state of technical competency and adherence to laboratory protocols across three individual hospital-affiliated Shanghai TB laboratories, and to identify areas of improvement for external quality assurance (EQA) by the Shanghai CDC.

Technicians at three Shanghai clinical laboratories were observed over two weeks. The laboratories varied greatly in their patient volume, ranging from fewer than 5 to more than 200 sputum samples per day, and their methods of testing, from Ziehl-Neelsen staining and solid culture medium, to Auramine O staining and liquid culture using the MGIT system. Although individual technician errors were found during comparison with protocol checklists at each laboratory, the most notable deviations were due to lack of funding or equipment, leading to makeshift substitutions for equipment, reagents, or personal protective equipment. Other issues included insufficient internal controls, lack of adherence to time-sensitive steps, and biosafety. Interestingly, technicians observed appeared to be competent, efficient, and experienced, and understood correct protocols but justified deviations due to personal experience and constraints in funding or time.

Fortunately, reliable methods of TB diagnosis exist, and new rapid diagnostic tools are now available. However, use of these tools, particularly in low-resource settings, is limited by appropriate infrastructure, quality management systems, and strategies and funding for laboratory staff development. Looking forward, resolution of issues identified in this project will likely require greater stringency in current EQA systems, additional laboratory funding, and the development of periodic required re-training programs.

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SINGLE VS. MULTIPLE FRACTIONATIONS IN THE TREATMENT OF VESTIBULAR SCHWANNOMAS WITH CYBERKNIFE STEREOTACTIC RADIOSURGERY

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Vestibular schwannomas are benign, schwann-cell derived tumors arising from the vestibulocochlear nerve sheath that can cause progressive unilateral sensorineural hearing loss, balance disorders and tinnitus. Current treatments include microsurgery, single fraction stereotactic radiosurgery (SRS) and multiple fraction stereotactic radiotherapy (SRT). While radiation is less invasive, it also frequently results in a decrease in hearing preservation, thus various predictors and types of therapy have been explored to determine how to best preserve hearing in patients treated for vestibular schwannomas.

To determine the differences in outcome after STS vs. SRT, we retrospectively reviewed and compiled data from 200 patients from Stanford University's CyberKnife Center and 541 patients from the German CyberKnife Clinic. Existing data from serial MRI's, patient notes and audiology reports is in the process of being analyzed to determine whether a difference in 1) tumor reduction 2) side effects involving cranial nerve VII 3) or cranial nerve VIII exist after SRS vs. SRT. Due to discrepancies in data collection, the present analyses are limited to single institutional analyses. First, the Kaplan Meier curve for GammaKnife and CyberKnife technology for tumor control at the German Clinic has demonstrated improved tumor control in patients treated with GammaKnife. Second, initial analysis of cranial nerve VII for facial palsy post-radiosurgery in 156 Stanford patients is inconclusive as only two patients have undergone single fraction radiosurgery. Third, a Kaplan Meier curve comparing regression to bad hearing (PTA >60 dB) in 541 patients treated at the German Clinic demonstrated longer maintanence of good hearing post-surgery in those treated with GammaKnife.

Preliminary results are inconclusive as we have not been able to combine data between both institutions. We are currently in the process of compiling the last of the raw data from both the Stanford and German databases and thus complete analyses are still being performed.

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ACUTE LUNG INJURY IN PATIENTS WITH SUBARACHNOID HEMORRHAGE: A NATIONWIDE INPATIENT SAMPLE STUDY

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Subarachnoid hemorrhage (SAH) causes significant morbidity and mortality. Pulmonary complications may be particularly frequent, but national data is lacking on the outcomes associated with acute respiratory distress syndrome (ARDS) in SAH patients. The aim of this study is was to determine national trends for SAH patients with ARDS.

The Nationwide Inpatient Sample Database (NIS) was utilized to sample 394,464 admissions for SAH with and without ARDS from 1993 to 2008 using ICD-9-CM coding. The incidence of ARDS in SAH has increased from 28.4% in 1993 to 34.4% in 2008. However, the overall mortality in SAH patients and in SAH patients with ARDS has decreased in the same period, from 30.5% to 21.2% and from 67.2% to 46.0% respectively. Multivariate analysis showed that the predictors of developing ARDS in SAH patients include older age, female gender, ethnicities other than white, larger hospital size, and comorbidities such as epilepsy, cardiac arrest, sepsis, congestive heart failure, hypertension, chronic obstructive pulmonary disease, and hematologic, renal, neurological, or liver dysfunction. Predictors of mortality in SAH patients include age, female gender, and hospital complications such as coronary artery disease, ARDS, cancer, and hematologic, renal, or liver dysfunction. The mean length of hospital stay was 24 days in SAH patients with ARDS, compared to 12 days in SAH patients without ARDS ($p < 0.001$).

The prevalence of ARDS in patients with SAH may be higher than previously reported and has increased from 1993 to 2008. The identification of certain risk factors may alert and aid the practitioner in preventing worsening disease.

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IMPAIRMENT OF AXONAL TRANSPORT AFTER ACUTE EXPERIMENTAL ANTERIOR ISCHEMIC OPTIC NEUROPATHY

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Anterior ischemic optic neuropathy (AION) is due to ischemia of the optic nerve head, leading to significant vision loss. While the pathogenesis of AION is not well understood, impairment in axonal transport may be a significant early event in the degeneration of retinal ganglion cells. To study changes in axonal transport after ischemia, we used a laser-assisted photochemical thrombosis model of AION in adult mice. We performed bilateral intravitreal injections of fluorescent cholera toxin B (CTB-A488) or $MnCl_2$, tracers known to be transported along axons, 2 hours after inducing ischemia and measured transport from the eye to the brain through the optic nerve 24 hours later using traditional histology or manganese-enhanced magnetic resonance imaging (MEMRI), respectively.

After ischemia, there was significant impairment of anterograde transport of CTB-A488 from the eye to the superior colliculi and lateral geniculate nuclei in the brain through the optic nerve ($N = 19$ mice, $P < 0.0001$), similar to that seen following intravitreal injection of colchicine, a known inhibitor of microtubule function and axonal transport. To assess axonal transport in the central nervous system *in vivo*, we developed the technique of MEMRI in mouse using a 7 Tesla MRI. We imaged the anterograde transport of manganese to the brain using T_1- and T_2-weighted sequences, utilizing a mouse brain template to perform three-dimensional reconstruction and quantification. Using MEMRI, we showed that axonal transport in the retinal ganglion cells was disrupted within hours following ischemia.

We demonstrated for the first time that anterograde axonal transport is severely impaired within 2 hours after optic nerve head ischemia using cholera toxin B A488 and Mn2+-enhanced MRI. Future studies will investigate whether axonal transport is more impaired in older mice, as AION predominantly afflicts patients over age 50.

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CAPECITABINE-UREA CYCLE ENCEPHALOPATHY: A PROSPECTIVE STUDY IN GI CANCER PATIENTS ON COMBINATION CHEMOTHERAPY

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The primary purpose of the study is to diagnose encephalopathy that may result from treatment with the chemotherapy drug capecitabine. We hypothesize that in the setting of a partial urea cycle defect, capecitabine inhibits an alternate pathway of ammonia clearance in the body leading to hyperammonemia that may contribute to CNS dysfunction. Even though urea cycle defects are relatively rare, the carrier frequency for mutations in the genes involved in the urea cycle is about 5%, which implies that the prevalence of partial urea cycle defects, and hence encephalopathy in patients on capecitabine is more common than is currently thought. In order to uncover possible capecitabine/urea cycle encephalopathy in patients with GI cancers we used serum ammonia levels as a biochemical marker for encephalopathy with the goal that it may be used as a diagnostic marker for this drug-induced encephalopathy.

We enrolled patients that were either already on or newly prescribed capecitabine as part of their treatment at the Stanford GI Oncology clinic. After chart review of upwards of 200 patients in the clinic, 64 were recruited into the study of which 36 patients had sufficient ammonia levels drawn to be included in the final analysis*. In a subset of 8 patients who were on a 7 day-on, 7-day off cycle the mean change in plasma ammonia levels around day-7 of the 14-day cycle was **– 2.72 ± 12.48** (mean ± SD) with 95% confidence interval of the net change being **-11.37 to 5.93.** In the second subset of 18 patients on a 14-day on, 7-day off cycle the mean change in plasma ammonia levels around day-14 of the 21-day cycle was **– 4.33 ± 10.99** (mean ± SD) with 95% confidence interval of the net change being **-9.40 to 0.75**. Of the 6 patients in this sub-group with bumps in day-14 ammonia, 2 patients reported their thinking being affected during the chemotherapy cycle.

While built on a strong theoretical framework, given the complexity of the patient population in terms of disease characteristics, varied extents of hepatic involvement, and the multi-drug regimens the study did not detect an obvious bump in ammonia levels on average in the patients who completed the study. A major issue in this analysis is the heterogeneity of the patient population and the small percentage of patients in which we expect the change. While routine measurement of plasma ammonia for all patients taking Xeloda as part of a multi-drug therapy may not be necessary, this marker continues to remain a mainstay of diagnosing hepatic encephalopathy. Patients who are on Xeloda/5-FU as part of their treatment regimens should be routinely assessed for symptoms of fatigue, lethargy, drowsiness or changes to mental status different from their baseline. It is these subset of patients on which plasma ammonia should be obtained to evaluate for possible ammonia-induced encephalopathy.

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*Data from 10 patients in the study on Single-Agent Capecitabine + Radiation therapy analyzed separately by co-study investigator Kevin Ch

STUDENT PERCEPTIONS ON STANDING-DESKS IN THE CLASSROOM: IMPLICATIONS FOR STUDENT LEARNING, WELLNESS, AND HEALTH

Casey Means, Dr. Clarence Braddock. Department of Medical Education.

Recent literature in the field of “Inactivity Studies” suggests that the extensive time Americans spend sitting contributes to poor health, chronic disease, early mortality, and reduced productivity. While some schools and companies have responded to this data by incorporating standing-desks in their facilities, no research to date has analyzed how this infrastructure affects learning, cognitive performance, and wellness. Survey data obtained at Stanford Medical School in 2011 suggests that pre-clinical students spend a significant amount of time sitting in classrooms, and as such are predisposed to the myriad ill effects associated with sedentary behavior. This research pilot qualitatively examined how the incorporation of standing-desks in pre-clinical classrooms affects the student learning experience.

30 second-year medical students were recruited to use standing-desks during a 3-hour pre-clinical seminar in March 2012. Students were subsequently engaged with questions about the experience in a focus group. 100% of students who were recruited agreed to participate in the study. Focus group transcripts were analyzed for perceptions regarding the relationship between standing in the classroom and various qualitative measures of learning experience.

Three major findings arose from this pilot. First, a majority of students believe that standing, in comparison to sitting, promotes attention and alertness in class. Second, many students believe that standing creates a dynamic learning space which fosters effective interpersonal interaction between students. Third, a majority of students assert that the incorporation of standing-desks in classrooms would be a positive addition to the pre-clinical medical school learning experience.

The results of this pilot study may serve as a foundation for modernizing the existing pedagogical dogma that students should sit in the classroom, and help to encourage the adoption of healthier and more effective learning environments.

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DIVERGENT PATTERNS OF INCIDENCE IN PERIPHERAL NEUROBLASTIC TUMORS

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Prior research on trends in pediatric neuroblastoma incidence has conflicted. However, few studies used comprehensive, population-based registries. We aimed to determine how peripheral neuroblastic tumor (ganglioneuroblastoma and neuroblastoma) incidence has changed. Using the Surveillance Epidemiology and End Results (SEER 9) population-based registry, we identified 2,081 peripheral neuroblastic tumors (pNT) in patients 0-14 years from 1973-2009. Age-adjusted incidence rates were calculated using SEER*Stat, and Joinpoint Regression Program was used to calculate annual percent change (APC) and analyze trends. Data were stratified by histology (ganglioneuroblastoma vs. neuroblastoma), age (<1 year vs. 1-14 years), and stage (locoregional vs. distant).

pNT incidence increased by an APC of 0.47 ($p < 0.05$). However, ganglioneuroblastoma incidence decreased (APC = -1.48; $p < 0.01$), while neuroblastoma incidence increased (APC = 0.79; $p < 0.01$). When divided by age and stage, pNT incidence in infants with locoregional disease increased until a significant inflection point in 1996 (APC = 3.68; $p < 0.01$), and then decreased sharply (APC = -7.81; $p = 0.11$, Figure). All other age and stage sub-groups showed non-significant increases.

Ganglioneuroblastoma incidence has decreased while neuroblastoma incidence has increased. These changes could be real, e.g., neuroblastoma incidence paralleling increasing birth weight, or could reflect bias from changes in classification or increased detection. pNT incidence increased most markedly in infants with locoregional disease only until 1996, perhaps suggesting increased tumor ascertainment during an era when screening programs raised awareness of pNT.

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COMMUNICATION CHALLENGES IN CLINIC: STUDENT PERSPECTIVES

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Excellent communication is essential for effective doctoring. Doctors in practice are often found lacking in fundamental skills. Much attention has therefore focused on the development and assessment of medical student knowledge and skills. Since the Kalamazoo consensus statement, curricula and assessments have focused on the essential elements of medical communication. We are proactively addressing this issue, yet little is known about the communication challenges students experience on their clinical clerkships. This poster presents quantitative and qualitative analysis of 3 years' (n = 250) of student patient logs describing communication challenges experienced while on their Family Medicine clerkship. Students on their Core Family Medicine clerkship were required to log one salient communication challenge or surprise. Comments are analyzed thematically and recommendations for curriculum development are suggested.

A MENDELIAN RANDOMIZATION ANALYSIS DOES NOT SUPPORT A CAUSAL ASSOCIATION BETWEEN TYPE 2 DIABETES AND PROSTATE CANCER

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Type 2 diabetes (T2D) has been consistently shown to decrease the risk of prostate cancer in epidemiological studies. It has been hypothesized that insulin concentrations, a defining aspect of the T2D disease process, are the specific mechanism by which T2D modulates cancer risk. However, T2D and cancer share a number of common risk factors that could confound epidemiological studies. When a randomized controlled trial is not feasible, Mendelian randomization is one approach that can be used to account for known and unknown confounders in order to make causal inferences between an exposure and outcome. Here we test the hypothesis that a genetic predisposition to T2D, or to elevated fasting insulin concentrations (FI), is associated with prostate cancer risk. Forty-nine T2D and eighteen FI risk variants were identified from genome-wide association study (GWAS) meta-analyses. *In silico* analysis of GWAS data was conducted to examine the association of individual variants with prostate cancer. A weighted summary statistic risk score method was used in the primary analysis to determine the OR of cancer per genetically predicted increase in either the log odds of T2D or log FI.

The T2D risk increasing allele (G) of *HNF1B* rs4430796 was associated with a reduction in prostate cancer risk (OR, 0.72; 95% CI, 0.66-0.79). The weighted T2D risk score was not significantly associated with the risk of prostate cancer (P=0.195). However, the FI risk score demonstrated a borderline significant decrease in risk of prostate cancer (OR, 0.86; 95% CI, 0.74-1.01; P=0.062) per genetically predicted 0.1 unit increase in log FI.

These data do not support an association between type 2 diabetes and prostate cancer despite evidence from epidemiological studies. Additionally, our analysis suggests that insulin levels may be causally associated with prostate cancer risk. However, larger studies with more power are needed.

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A COGNITIVE AID "CENTRAL LINE CARE CARD" FOR CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTIONS (CABSIs) IN PEDIATRIC HOME TOTAL PARENTERAL NUTRITION (TPN) PATIENTS

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Catheter associated bloodstream infections (CABSIs) are associated with serious morbidity, mortality, and economic costs, but management and outcomes of CABSIs in pediatric home total parenteral nutrition (TPN) patients have not been well studied. We propose a novel cognitive aid containing information for both medical professionals and patient families, a "Central Line Care Card," as an intervention for pediatric home TPN patients. This prospective, open-label, cohort study of long term TPN patients at Lucile Packard Children's Hospital (LPCH) Gastroenterology (GI) Clinic examines if the cognitive aid can improve management of CABSIs and patient family satisfaction with central line associated medical encounters.

28 long term TPN patients ages 0-25 were given personalized care cards that indicated the patient's diagnosis, details about the central line, and instructions for the parents and medical providers when a patient presented to a medical facility with a fever and potential CABSI. We then tracked the medical management of care when a patient presented with a fever and potential CABSI. 14 healthcare visits due to fever have been analyzed to date and have trended toward decreased breaches in care of potential CABSIs after implementation of the care card. Pre- and post-intervention, LPCH had no breaches in care, while outside hospitals (OSH) breached care in 36% of visits pre-intervention. With 4 visits to date post-intervention, OSH breached care in 25% of visits. Qualitative parent surveys indicated positive, enthusiastic response to the personalized Care Cards. When the card was shown to a healthcare professional, parents reported that the card impacted their experience "extremely" or "a great deal" positively (out of "1-extremely," "2-a great deal," "3-moderately," "4-slightly," "5-not at all").

The data trend toward reducing breaches in care of potential CABSIs suggests that this extremely low-cost intervention may quickly improve management of potential CABSIs at lower-level healthcare centers that rarely encounter children on home TPN. With an estimated attributable mortality of 12% to 35% per CABSI, and 1-3 CABSIs/1000 catheter days, this may amount to a significant reduction in mortality as well as morbidity and healthcare costs, all while improving patient family satisfaction. Further studies are needed to test the generalizability of these findings to other regions and other indications for a long-term central line such as chemotherapy.

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SHORT-TERM CONSTIMULATORY MOLECULE BLOCKADE PROMOTES LONG-TERM ENGRAFTMENT OF TRANSPLANTED HUMAN EMBRYONIC STEM DERIVATIVES AND IMPROVES CARDIAC RECOVERY

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Transplantation of human embryonic stem cells (hESC) and their derivatives offers great promise in preventing cardiac failure following acute myocardial infarction. However, transplantation requires effective long-term immunosuppression which is problematic due to toxicity of traditional drugs, e.g. Cyclosporine A (CsA). Here, we test the hypothesis that briefly blocking costimulatory molecule signaling with two agents (anti-LFA-1 and CTLA4-Ig) promotes cell survival and improves functional outcome of transplanted hESC-derived endothelial cells (hESC-ECs) after myocardial infarction.

Human ESC-ECs were stably transduced with GFP-Fluc for fluorescence and bioluminescence imaging (BLI). $2x10^6$ cells were injected into the left ventricle of immunocompetent (FVB) and immunodeficient (SCID) mice following LAD ligation. Animals were randomized to receive either no immunosuppression, a standard approach (CsA and prednisone), or a short course of costimulatory blocking agents. In the absence of immunosuppression or after standard therapy, transplanted cells were rejected by day 14 after transplantation. In contrast, combined treatment with CTLA4-Ig and anti-LFA enhanced cell engraftment and was associated with improved myocardial function assessed by MRI and echo. In a Matrigel plug assay, the same survival patterns were observed. Histological analyses revealed minimal immune cell infiltration and significantly more angiogenesis in the group receiving costimulatory agents. Flow cytometric analysis showed equivalent levels of circulating T cells in all groups, but $CD4^+$ helper T cell infiltration into the Matrigel plugs of animals receiving costimulatory blockade was lower than in those treated with CsA + prednisone.

A short immunosuppressive course of costimulatory blockade is sufficient to induce engraftment of transplanted hESC-ECs associated with attenuated cardiac remodeling. This approach is beneficial, because it circumvents the chronic administration and systemic toxicity associated with traditional immunosuppressive drugs.

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A PROSPECTIVE LOOK AT PROBIOTICS: COMPILING LESSONS FROM PREVIOUS INTVENTIONS TO INFORM A TRIAL ON THE SAFETY AND EFFICACY OF PROBIOTS IN BANGLADESHI INFANTS

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Stunting in childhood is linked to developmental delays and increased mortality. One plausible contribution to stunting is the gut microbiota, which normally stimulates immunity, breaks down nutrients, and prevents pathogen colonization. Probiotics have been shown to increase weight in low birth weight infants and prevent acute diarrhea. They represent an opportunity for novel interventions in low-income settings.

A number of probiotic strains have been shown to be safe in infants and children in the United States. They have been used to increase weight in low birth weight children, prevent acute diarrhea and necrotizing enterocolitis (NEC), and they have shown promise in the treatment of several conditions. Prior to the commencement of a trial of probiotics among infants in Bangladesh, I am conducting a literature review of relevant nutrition interventions to assemble an initial proposal for a future, larger-scale intervention. This proposal will augment the initial stages of project design and implementation by providing insights into the challenges and logistics of a larger-scale intervention.

Beginning this summer, we will use existing infrastructure at the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B) to conduct a modified Phase-I trial of probiotics in Bangladeshi infants. We will recruit 150 infants 1-3 months of age and randomize participants into one of three probiotic dosage arms; a control arm will receive no probiotics. The specific aims of this study are to 1) investigate the safety of probiotics 2) preliminarily assess physiologic, microbiologic, and immunologic effects, and 3) evaluate the effect of probiotic administration on breastfeeding behaviors. These aims, combined with background research on projects in other settings, will allow us to assemble a project proposal for future, larger-scale intervention.

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PHYSICIAN-FAMILY COMMUNICATION IN THE PEDIATRIC INTENSIVE CARE UNIT

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Communicating effectively with families is one of the most important roles of the pediatric critical care physician. However, insufficient data exist regarding best practices for pediatricians to use while communicating with families during difficult conversations in the pediatric intensive care unit (ICU). Qualitative research on physician-family communication in the adult ICU is abundant. In contrast, little empirical study has been done around physician-family communication in the pediatric ICU. To date, there are no published studies that explore the actual conversations that occur between physicians and families during care conferences in the pediatric ICU. We audio-recorded and transcribed 20 family care conferences in the pediatric ICU and pediatric cardiovascular ICU at Lucile Packard Children's Hospital at Stanford. We included conversations conducted in English and those conducted with the assistance of an in-person Spanish interpreter. Using the principles of grounded theory, we coded and analyzed the conversations for both content and style of communication. Grounded theory offers systematic procedures that move from description to analysis, and enables theories to be developed inductively.

Analysis began with open coding of the transcripts, leading to an inductively-derived coding scheme. This analytic approach is well-suited to identifying emerging themes or categories of information within qualitative text data, and for developing theories about the phenomenon described by these themes. Families also completed a short satisfaction survey, which we correlated to various communication styles. Differences in communication content, style, and family satisfaction were compared between English-speaking families and Spanish-speaking families. Further analysis is currently underway.

With this data, we evaluate the ways in which attending physicians in our pediatric intensive care units communicate with families regarding their critically ill infants and children, and provide additional data toward the formation of best practices for physician-family communication in the pediatric ICU setting.

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CEREBRAL OXYGENATION AND AUTOREGULATION IN PRETERM INFANTS: ASSOCIATION WITH MORBIDITY AND MORTALITY

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Background: Extremely preterm infants are at risk for hemodynamic instability and impaired cerebral autoregulation, a process that keeps cerebral blood flow constant over varying systemic blood pressures. When this mechanism fails, there may be increased periods of pressure passive blood flow, which could lead to the development of neurologic injury, especially in the immature preterm brain. Near infrared spectrometry (NIRS) is a non-invasive, bedside device that allows measurement of tissue oxygen perfusion. In this pilot study we use NIRS to measure cerebral blood flow in preterm infants for the first days of life to 1) determine whether NIRS measurements are effective indicators of mortality or development of CNS morbidity, including intraventricular hemorrhage (IVH) or white matter injury, and 2) correlate the degree of cerebral pressure passivity with mortality and development of CNS morbidity.

Methods: A NIRS neonatal sensor was placed on the forehead of eligible infants (birth weight <1250 grams, age <24 hours) and regional oxygen saturation (rSO_2) readings and mean systemic blood pressure measurements were obtained every minute for 96 hours of life.

Results: Twelve infants have been enrolled with mean weight of 856.2 grams, gestational age of 27.3 weeks, and APGAR scores of 4.7 and 7.3 at one and five minutes, respectively. Pressure passivity index (PPI), defined as the percentage of time of rSO_2 and mean arterial blood pressure concordance, was an average of 12% (SD=10.5%). Four infants have had signs of IVH by cranial ultrasound, one of whom died prior to hospital discharge. Three of the four with poor neurologic outcomes had high PPI levels, i.e. they were in a pressure passive state with loss of cerebral autoregulation for >20% of time on study. This research is ongoing and preliminary analyses presented in May will include mixed-effect linear regression to assess the relationship between NIRS measurements of low rSO_2 and PPI with CNS morbidity and mortality.

Conclusion: If analyses suggest that NIRS measurements and PPI can be used reliably to detect preterm infants at risk for neurologic injury, we could use this information to counsel families and potentially stage early interventions to improve prognoses.

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COST-EFFECTIVENESS OF SHOULDER ARTHROPLASTY FOR MASSIVE IRREPARABLE ROTATOR CUFF TEARS

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Massive irreparable rotator cuff tears result in shoulder pain and dysfunction. Established interventions, such as physical therapy (PT) and arthroscopic debridement with biceps tenotomy (AD-BT), have traditionally focused on pain reduction and quality-of-life improvements. However, hemiarthroplasty (HA) and reverse total shoulder arthroplasty (RTSA) are more invasive surgical treatment options that may offer better functionality gains. Recent studies suggest that RTSA leads to superior clinical outcomes compared to all other management strategies, but the procedure comes with greater costs as well as higher complication and reoperation rates.

We developed a Markov decision model to compare, from the societal perspective, the cost-effectiveness of PT, AD-BT, HA, and RTSA as management strategies for massive irreparable rotator cuff tears. Outcome probabilities and utilities were derived from the literature, and costs were estimated from national average Medicare reimbursement data from 2011. Our base case scenario was that of a 70-year-old female patient with 120 degrees of active forward elevation of the arm. AD-BT was more cost-effective than PT, and HA was slightly more cost-effective than RTSA by providing higher number of average QALYs at lower average costs.

While HA was more effective than AD-BT, the incremental cost-effectiveness ratio of ~$330,000/QALY between the two interventions is well above the standard willingness-to-pay threshold of $50,000/QALY. Sensitivity analysis revealed that RTSA will dominate HA with a 10% decrease in costs or a 6% increase in QALYs, and that AD-BT is the most cost-effective management strategy unless QALY gains over baseline are reduced by 70% to levels below all other treatment options. These findings suggest that AD-BT is the optimal cost-effective treatment option for elderly patients with massive rotator cuff tears. There was no statistically significant difference between RTSA and HA.

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SUTURE BUTTON SUSPENSION FOLLOWING TRAPEZIECTOMY IN A CADAVER MODEL

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The safety and the effects of different trajectories on thumb motion of suture-button suspensionplasty post-trapeziectomy are not known. In a cadaveric model, thumb range of motion, trapeziectomy space height, and distance between the device and nerve to the first dorsal interosseous muscle (1st DI) were measured for proximal and distal trajectory groups.

There were no significant differences in range of motion and trapeziectomy space height between both groups. The device was significantly further away from the nerve to the 1st DI in the proximal trajectory group compared to the distal trajectory group, but was still safely away from the nerve in both groups (greater than 1 cm).

These results suggest that the device placement in either a proximal or distal location on the second metacarpal will yield similar results regarding safety and thumb range of motion.

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AN ENGINEERED KNOTTIN PEPTIDE FOR OPTICAL IMAGING OF MEDULLOBLASTOMA

Sarah J. Moore, Melanie GH Gephart, Jamie M. Bergen, YouRong **Sophie Su**, Helen Rayburn, Matthew P Scott, Jennifer R. Cochran

Central nervous system tumors carry grave clinical prognoses due to limitations in surgical resection, radiation, and chemotherapy. Improved strategies are needed for tumor imaging, resection, and targeted treatment. We demonstrate that mouse medulloblastoma (MB) can be targeted and illuminated with an engineered cystine-knot (knottin) peptide that binds to αvβ3, αvβ5, and α5β1 integrin receptors. Denoted as EETI 2.5F, this knottin was evaluated as a molecular imaging probe in both orthotopic and genetic models of MB. Following tail vein injection, fluorescent EETI 2.5F was localized preferentially to the tumor. The intensity of the imaging signal correlated with tumor size. EETI 2.5F was then fused to an antibody Fc domain (EETI 2.5F-Fc) to see if molecular size affected tumor targeting. EETI 2.5F-Fc similarly illuminated MB and distributed throughout the tumor parenchyma. In contrast, imaging signals were not detected in brain tumors injected with EETI 2.5F proteins containing a scrambled integrin-binding sequence, demonstrating the importance of target specificity.
Our results highlight knottins as promising molecular probes for tumor imaging.

IN-VITRO AND IN-VIVO MODELS OF HUMAN PSORIASIS

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Psoriasis is a chronic inflammatory immune-mediated skin disease with a prevalence of 2-3% worldwide. Psoriasis is characterized by abnormal differentiation and hyperproliferation of keratinocytes and skin-infiltrating inflammatory immunocytes. The role of keratinocytes in the initiation and maintenance of inflammation in psoriasis remains unknown.

To determine the role of keratinocytes in psoriasis, a novel keratin-14 driven activated (V12) Rac1 (Rho GTPase) mutant in transgenic mouse epidermis was genetically engineered, which closely mimics human psoriasis phenotype. From these findings, we hypothesize that psoriasis arises from heterologous defects that share a hyperactive epidermal-immune signaling loop arising in response to minor trauma or other normal physiologic stimuli. To further study the individual contributions of cellular constituents to the disease process, we created in-vitro skin equivalent system and in-vivo human xenograft model using genetic manipulation of primary human keratinocytes.

Retroviral transfections of primary human keratinocytes (KCs) with Rac1 or LacZ (control) genes were performed. For in-vitro skin equivalent system, Rac1 or LacZ overexpressed transduced KCs were seeded onto devitalized dermis and cultured to confluence. Skin equivalents were then placed at the air-fluid-interface and allowed to differentiate with or without (non)-stimulated human peripheral blood mononuclear cells (PBMCs). For in-vivo xenograft model, skin equivalents were grafted on Non-obese Diabetic/Severe Combined Immunodeficient (NOD/SCID)-mice and injections of saline or (non)-stimulated PBMCs were performed at 1-week and 2-week post-surgery.

From immunohistochemistry and immunofluorescence studies, both in-vitro and in-vivo models have reproduced certain features of psoriasis including acanthosis, papillomatosis, and dermal cellular infiltrates. The versatile model systems we have developed allows for specific targeted gene knock-down studies using small-interfering RNA (siRNA) in keratinocytes to inhibit epidermal-immune signaling pathways allowing for determination of pathophysiology of disease and providing avenues for development of keratinocyte-specific topical therapies that may reduce side effects associated with systemic immunosuppressive therapies.

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PREDICTING MORTALITY AMONG HOSPITALIZED CHILDREN WITH RESPIRATORY INFECTION IN WESTERN KENYA

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To develop a respiratory severity index (RSI) score by identifying easy to monitor syndrome-based risk factors for in-hospital mortality in children aged under five years that were hospitalized with a respiratory illness in Siaya District Hospital (SDH) in western Kenya.

We analyzed data from children with respiratory illnesses (defined as acute onset of cough or difficulty breathing within the last 14 days) who were hospitalized at SDH between August 2009 and July 2012. A multivariable logistic regression model for mortality was developed using demographic characteristics and clinical signs and symptoms at admission. Points were assigned to risk factors based on their coefficients in the multivariable model. The RSI score for each child was developed by summing points for each risk factor present. Discrimination was evaluated using the concordance (or *c*) statistic. Using bootstrap samples, with 500 replications we re-estimated the coefficients and their corresponding 95% confidence intervals (CIs) as well as the optimism of the model.

We analyzed data from 3,581 respiratory hospitalizations including 218 (6%) respiratory deaths (median age 12 months, 54% male). History of unconsciousness (aOR=2.4; 95% CI 1.6-3.5), inability to drink or breastfeed (aOR=2.0; 95% CI 1.3-3.0), chest wall in-drawing (aOR=2.1; 95% CI 1.5-3.1), not alert on physical exam (aOR=8.6; 95% CI 5.5-13.4), low weight-for-age (aOR=2.1; 95% CI 1.4-3.2), very low weight-for-age (aOR=3.9; 95% CI 2.8-5.5) and admission diagnosis of dehydration (aOR= 2.0; 95% CI 1.4-2.8) were positively associated with in-hospital mortality. The RSI score ranged from -2 to 7. The positive predictive value for mortality increased with increasing RSI scores from 6% at a cut-off score of ≥-2 to 80% for patients with a cut-off score of ≥6. The prediction model also showed good discriminating power, as measured by c-statistics of 0.852 in the original dataset a 0.854; 95% CI 0.828 – 0.879 in 500 bootstrap samples.

ARSI score based on a set of easily measurable signs and symptoms at admission was able to predict children who were at greater risk of death from respiratory illness. Use of these scores could help identify high-risk respiratory patients at the time of admission so that clinical care for these patients could be prioritized early.

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APOLIPOPROTEIN E, GENDER, AND ALZHEIMER'S DISEASE: AN OVERLOOKED, BUT POTENT AND PROMISING INTERACTION

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Alzheimer's disease (AD) is an increasingly prevalent, fatal neurodegenerative disease that has proven resistant, thus far, to all attempts to prevent it, forestall it, or slow its progression. In the wake of two large, costly, and negative phase III studies of antibodies against beta-amyloid, there is a critical need for novel approaches to understanding AD and developing alternative targets for treatment. The ε4 allele of the Apolipoprotein E gene (APOE4) is a potent genetic risk factor for sporadic and late-onset familial AD[1-3]. While the link between APOE4 and AD is strong, many expected effects, like increasing the risk of conversion from MCI to AD, have not been widely replicable. One critical, and commonly overlooked, feature of the APOE4 link to AD is that several lines of evidence suggest it is far more pronounced in women than in men. This finding, despite its strength, and its having been replicated multiple times across sundry modalities, is almost never considered or investigated in clinical AD research where male and female APOE4 carriers are generally viewed as having equal risk. Here we review previous literature on the APOE4 by gender interaction, with a particular focus on imaging-related studies, while arguing that the fuller understanding of this interaction has the potential to yield sorely needed insights into AD pathogenesis.

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DOES CULTURE PLAY A ROLE? EXPLORING FACTORS THAT IMPACT A WOMAN'S PREFERENCE FOR AN EPIDURAL FOR PAIN RELIEF DURING LABOR

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Epidural use for pain relief during labor differs across ethnic/racial groups. Non-Caucasian women tend to receive fewer epidurals compared to Caucasians, however there is inadequate data to explain this difference. Language barriers may play a role, as well as partner preferences for the laboring woman. Prior studies on the topic are limited in that they employ convenience sampling, non-validated surveys, retrospective study designs, and/or small or limited samples (e.g. English-speaking only). Our study examines cultural, demographic, and clinical factors that influence a laboring woman's *a priori* desire to have an epidural for pain control.

We created and validated an online survey of non-clinical factors possibly associated with epidural use. Participation in the survey is being offered to all women admitted to Lucile Packard Children's Hospital for labor and delivery over a one-month period. A chart review is being used to obtain clinical data and match it with survey responses. Findings will be analyzed using multivariate analysis for predictors of epidural preference and actual use. Results will also be compared for differences across ethnic groups using Chi-squared testing.

We hope the results of the study will offer clinicians an improved framework from which to offer education and care such that patients of all ethnicities have an equivalent opportunity to make a decision about epidurals for labor.

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SCHEDULED IBUPROFEN PLUS ACETAMINOPHEN PROVIDES BETTER POST-CESAREAN ANALGESIA THAN SCHEDULED IBUPROFEN ALONE

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Scheduled NSAIDs in combination with scheduled acetaminophen provides better post-surgical analgesia than medication taken on an as-needed (prn) basis. The new recommended maximum daily dose of acetaminophen is 3 g. Recently the post cesarean section pain management protocol at Lucile Packard Hospital was changed accordingly. Prior to the change (Group 1), patients who were not at risk of bleeding were given IV ketorolac prn and offered 600 mg oral Ibuprofen every 6 hours for 48 hours after surgery. Break-through pain was managed with oral hydrocodone plus acetaminophen, oral oxycodone plus acetaminophen, or oral oxycodone prn. Intravenous morphine boluses were offered prn for undertreated pain. After the change (Group 2), patients were offered IV ketorolac prn, 600 mg oral Ibuprofen, and 650 mg oral acetaminophen every 6 hours for 48 hours after surgery. Oral oxycodone prn and then IV morphine boluses prn were used for undertreated pain. This study compared post-operative verbal pain scores, narcotic use, and side effects between the two groups.

120 patients were included in each group. Eligibility criteria were ≥ 18 years old, received a spinal or combined-spinal-epidural for the cesarean section, and had a term pregnancy (37 – 42 weeks gestation). Patients were excluded if they were ineligible to get ibuprofen or acetaminophen, were diagnosed with chorioamnionitis, or required a stay in the intensive-care unit. Intraoperative analgesia was the same between the two groups. There were no differences in baseline characteristics between the two groups ($P > 0.05$). Group 2 took significantly more acetaminophen than Group 1 ($P < 0.0001$). Total opioid use, as measured in IV morphine equivalents, was significantly less in Group 2 compared to Group 1 ($P < 0.001$). Verbal pain scores and medication side effects of pruritis, nausea, vomiting, and oxygen use were no different between the groups ($P > 0.05$).

This study shows that scheduled NSAIDs and acetaminophen together provide better postoperative analgesia than NSAIDs alone or medication given prn in patients after cesarean section.

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UNIVERSAL PRE-CONCEPTION CARRIER SCREENING FOR GENETIC DISEASE: A COST-EFFECTIVENESS ANALYSIS

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Single-gene disorders cause 20% of all infant deaths, and children with genetic disorders account for approximately 11% of pediatric hospital admissions. While the prevalence of each recognized single-gene defect is relatively low, the number of recognized genetic disorders is well over 15,000 and continues to grow. These diseases can be prevented or mitigated through carrier screening at the pre-conception stage, yet many carriers of disease have no family history and are not targeted for screening. Advances in genetic technology are making comprehensive carrier screening less expensive and more accessible, and screening tools now target a population-wide audience to screen for genetic disease.

This study evaluates the costs and benefits of the currently recommended screening protocol in the US for three genetic diseases including cystic fibrosis, spinal muscular atrophy, and sickle-cell disease against a universal pre-conception carrier test targeted to the US population. Analysis is performed using TreeAge Pro analysis software that takes into account several factors including accuracy of tests, disease penetrance and prevalence, difficult fertility decisions following a positive test, and risk of adverse outcomes. Sensitivity analysis determines thresholds for test cost, accuracy, and post-test behaviors. Preliminary results show the current pricing structure for tests exceeds its value from a societal perspective with regard to life years saved and reduced medical costs.

The clinical and financial implications of universal pre-conception carrier screening for genetic disease are unknown. Our ability to reduce the incidence of children born with genetic disease has been proven with the reduction of Tay Sachs in the Jewish population, but this has not been replicated with the same success with other genetic diseases. Might we be able to reduce and eventually eliminate inherited genetic disorders with a population-wide screening program and thus save significant medical expenditures, grief among family members and suffering to the individual? This research is useful for medical providers and administrators who must decide whether to offer such tests as well as to medical payers and policy makers who must determine whether to pay for it.

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INTERNATIONAL PREVALENCE OF INDOOR TANNING: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Indoor tanning is a known carcinogen, but the scope of exposure to this hazard is not known. Our goal was to summarize the prevalence of exposure to indoor tanning internationally.

We performed a systematic review using PubMed, Scopus, and Web of Science. Studies that reported a prevalence of the use of indoor tanning were eligible for inclusion. We excluded case-control studies, reports with insufficient study information, and reports of groups recruited using factors related to indoor tanning. Random-effects meta-analyses were used to summarize the prevalence of indoor tanning in different age categories. We calculated the population proportional attributable risk of indoor tanning in the United States, Europe, and Australia for non-melanoma skin cancer (NMSC) and melanoma.

Our search yielded 1976 unique records. After exclusions, 161 records were assessed for eligibility in full-text, and 88 records were included. The summary prevalence of *ever exposure* to indoor tanning was 35.7% (95% confidence interval 27.5% to 44.0%) for adults, 55.0% (33.0% to 77.1%) for university students, and 19.3% (14.7% to 24.0%) for adolescents. The summary prevalence of *past year exposure* to indoor tanning was 14.0% (95% confidence interval 11.5% to 16.5%) for adults, 43.1% (21.7% to 64.5%) for university students, and 18.3% (12.6% to 24.0%) for adolescents. These results included data from 406,696 participants. The population attributable risk ranged from 3.0% to 21.8% for NMSC and from 2.6% to 9.4% for melanoma. This corresponds to over 450,000 new cases of NMSC and over 10,000 cases of melanoma each year attributable to indoor tanning in the United States, Europe, and Australia.

Exposure to indoor tanning is very common in western countries, especially among young people. Given the large number of skin cancers attributable to indoor tanning, these findings highlight a major public health issue.

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ENGINEERED SIRPα VARIANTS AS UNIVERSAL IMMUNOTHERAPEUTIC ADJUVANTS TO ANTI-CANCER ANTIBODIES

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The ability of tumors to evade the immune system is an emerging hallmark of cancer, and new therapeutic strategies that direct immune responses against cancer cells show promise in experimental and clinical settings. Macrophages often extensively infiltrate tumors, and recent studies have identified CD47 as an anti-phagocytic “don’t eat me” signal that is highly expressed on many types of cancer to avoid macrophage-mediated destruction. Antibodies that block binding of CD47 to SIRPα, an inhibitory receptor on macrophages, greatly increase phagocytosis of cancer cells. However, antibodies have limited tissue distribution and can exert off-target effects due to Fc-mediated functions.

In this study, we aimed to improve CD47-targeting therapies by utilizing the single 14 kDa CD47-binding domain of SIRPα as a competitive antagonist to CD47. We found that wild-type SIRPα is a poor antagonist due its weak ~1 μM affinity for native CD47. Therefore, we exploited structural knowledge of the CD47-SIRPα interaction and performed in vitro evolution via yeast surface display to engineer high-affinity SIRPα variants. Biophysical measurements demonstrated the mutants had up to a 50,000-fold increase in affinity for CD47 relative to wild-type SIRPα. To our surprise, the high-affinity SIRPα variants potently antagonized CD47 on the surface of cancer cells but did not induce macrophage phagocytosis on their own. However, when combined with any tumor-specific monoclonal antibody, the high-affinity SIRPα variants led to dramatic increases in phagocytosis. In vitro, the high-affinity SIRPα variants enhanced the efficacy of rituximab (anti-CD20) against lymphoma, cetuximab (anti-EGFR) against colon cancer, and trastuzumab (anti-Her2) against breast cancer. Thus, CD47 blockade is not sufficient to induce phagocytosis, but instead lowers the threshold for macrophage activation in response to other pro-phagocytic stimuli such as antibody Fc. In vivo, addition of high-affinity SIRPα variants to rituximab led to a remarkable, synergistic anti-lymphoma effect. Nearly all mice treated with rituximab alone died a few weeks post-engraftment, but the majority of mice treated with the combination of rituximab and high-affinity SIRPα variants exhibited prolonged cures with no evidence of residual disease.

These findings deepen our understanding of the principles that govern macrophage activation against cancer. Moreover, since CD47 is a common mechanism that tumor cells use to evade the immune system, the molecules generated in this study could benefit many cancer patients as universal adjuvants to therapeutic antibodies.

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INVESTIGATING THE GENETIC AND MOLECULAR CHANGES IN FIBROLAMELLAR CARCINOMA

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Fibrolamellar carcinoma (FLC), a rare malignancy of adolescents and young adults, arises in noncirrhotic livers. FLC was originally described as a histological variant of Hepatocellular Carcinoma (HCC), however a different set of clinicopathologic features has defined it as a separate disease. The low incidence rate, 0.02 per 100,000, has kept FLC an understudied cancer – and its etiology and molecular pathogenesis remain unknown. Our goal is to understand the molecular mechanisms contributing to FLC development, in particular, the somatic mutations acquired during tumorigenesis. We hypothesize that FLC cells accumulate a distinct pattern of genetic changes compared to other liver tumors.

We have performed whole genome sequencing (WGS) and transcriptome sequencing on an index case, and to our knowledge, this is the first in-depth characterization of fibrolamellar carcinoma. WGS analysis has revealed a surprising lack of alterations in canonical tumor suppressors, such as TP53, PTEN, or RB1, and proto-oncogenes, such as KRAS or c-Myc. Interestingly, the index case has accumulated mutations involving DNA repair genes and genes in the Wnt/Beta-catenin signaling pathway. Transcriptome analysis confirms that the Wnt signaling pathway is upregulated and preliminary immunohistochemical analysis shows that FLC tumor cells contain more active beta-catenin than adjacent normal liver tissue. Additionally, transcriptome sequencing of the FLC case confirmed previous reports that FLC cells express not only hepatic markers, but also markers of both bile duct and neuroendocrine differentiation, suggesting that FLC arises from a population of early liver progenitors. Finally, by comparing the gene expression signature of FLC to previously published microarray datasets of hepatocellular carcinoma (HCC), we have identified potential novel biomarkers of FLC, which may help diagnose FLC patients.

Our current ongoing work focuses on validating these results across additional FLC cases to identify possible therapeutic targets for this pediatric cancer.

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