

References

Akcakaya, M., Peters, B., Moghadamfalahi, M., Mooney, A. R., Orhan, U., Oken, B., et al. (2014).

Noninvasive brain-computer interfaces for augmentative and alternative communication. *IEEE Reviews in Biomedical Engineering*, 7, 31-49.

Brain-computer interfaces (BCIs) promise to provide a novel access channel for assistive technologies, including augmentative and alternative communication (AAC) systems, to people with severe speech and physical impairments (SSPI). Research on the subject has been accelerating significantly in the last decade and the research community took great strides toward making BCI-AAC a practical reality to individuals with SSPI. Nevertheless, the end goal has still not been reached and there is much work to be done to produce real-world-worthy systems that can be comfortably, conveniently, and reliably used by individuals with SSPI with help from their families and care givers who will need to maintain, setup, and debug the systems at home. This paper reviews reports in the BCI field that aim at AAC as the application domain with a consideration on both technical and clinical aspects. © 2013 IEEE.

Alzhanova, D., Hammarlund, E., Reed, J., Meermeier, E., Rawlings, S., Ray, C. A., et al. (2014). T cell inactivation by poxviral b22 family proteins increases viral virulence. *PLoS Pathogens*, 10(5), e1004123.

Infections with monkeypox, cowpox and weaponized variola virus remain a threat to the increasingly unvaccinated human population, but little is known about their mechanisms of virulence and immune evasion. We now demonstrate that B22 proteins, encoded by the largest genes of these viruses, render human T cells unresponsive to stimulation of the T cell receptor by MHC-dependent antigen presentation or by MHC-independent stimulation. In contrast, stimuli that bypass TCR-signaling are not inhibited. In a non-human primate model of monkeypox, virus lacking the B22R homologue (MPXVDelta197) caused only mild disease with lower viremia and cutaneous pox lesions compared to wild type MPXV which caused high viremia, morbidity and mortality. Since MPXVDelta197-infected animals displayed accelerated T cell responses and less T cell dysregulation than MPXV US2003, we conclude that B22 family proteins cause viral virulence by suppressing T cell control of viral dissemination.

Amris, K., Waehrens, E. E., Jespersen, A., Stockmarr, A., Bennett, R., Bliddal, H., et al. (2014). The relationship between mechanical hyperalgesia assessed by manual tender point examination and disease severity in patients with chronic widespread pain: A cross-sectional study. *International Journal of Rheumatology*, 2014, 417596.

The clinical utility of tender point (TP) examination in patients reporting chronic widespread pain (CWP) is the subject of contemporary debate. The objective of this study was to assess the relationship between mechanical hyperalgesia assessed by manual TP examination and clinical disease severity. 271 women with CWP were recruited from a clinical setting. Data collection included patient-reported symptoms, health-related quality of life variables, and observation-based measures of functional ability, muscle strength, 6-minute walk, and pressure pain thresholds measured by cuff algometry. TP examination was conducted according to ACR-guidelines. Relationships between disease variables and TP count (TPC) were analyzed with logistic regression in a continuum model, allowing the TPC to depend on the included disease variables and two regression models carried out for a TPC threshold level, varying between 1 and 17. The threshold analyses indicated a TPC threshold at 8, above which a large number of disease variables became consistently significant explanatory factors, whereas none of the disease variables reached a significance level in the continuum model. These results support the premise that the presence of mechanical hyperalgesia influences symptomatology in CWP and that the severity of clinical expression is related to a threshold of TPs, rather than being part of a continuum.

Angier, H., Gold, R., Gallia, C., Casciato, A., Tillotson, C. J., Marino, M., et al. (2014). Variation in outcomes of quality measurement by data source. *Pediatrics*,

OBJECTIVE: To evaluate selected Children's Health Insurance Program Reauthorization Act claims-based quality measures using claims data alone, electronic health record (EHR) data alone, and both data sources combined. METHODS: Our population included pediatric patients from 46 clinics in the OCHIN network of community health centers, who were continuously enrolled in Oregon's public health insurance program during 2010. Within this population, we calculated selected pediatric care quality measures according to the Children's Health Insurance Program Reauthorization Act technical specifications within administrative claims. We then

calculated these measures in the same cohort, by using EHR data, by using the technical specifications plus clinical data previously shown to enhance capture of a given measure. We used the kappa statistic to determine agreement in measurement when using claims versus EHR data. Finally, we measured quality of care delivered to the study population, when using a combined dataset of linked, patient-level administrative claims and EHR data. RESULTS: When using administrative claims data, 1.0% of children (aged 3-17) had a BMI percentile recorded, compared with 71.9% based on the EHR data (kappa agreement $[k] \leq 0.01$), and 72.0% in the combined dataset. Among children turning 2 in 2010, 20.2% received all recommended immunizations according to the administrative claims data, 17.2% according to the EHR data ($k = 0.82$), and 21.4% according to the combined dataset. CONCLUSIONS: Children's care quality measures may not be accurate when assessed using only administrative claims. Adding EHR data to administrative claims data may yield more complete measurement.

Apolo, A. B., Kim, J. W., Bochner, B. H., Steinberg, S. M., Bajorin, D. F., Kevin Kelly, W., et al.

(2014). Examining the management of muscle-invasive bladder cancer by medical oncologists in the united states. *Urologic Oncology*,

BACKGROUND: Neoadjuvant chemotherapy (NACT) for the treatment of muscle-invasive bladder cancer (MIBC) remains underutilized in the United States despite evidence supporting its use.

OBJECTIVES: To examine the perioperative chemotherapy management of patients with MIBC by medical oncologists (MedOncs) to move toward standardization of practice PARTICIPANTS AND

METHODS: A 26-question survey was emailed to 92 MedOncs belonging to the Bladder Cancer Advocacy Network or the American Society of Clinical Oncology for completion from May to

October 2011 RESULTS: A total of 83 MedOncs completed the survey: 52% were based in

academic centers. Most referrals were from urologists (79%). NACT for treatment of MIBC and high-grade upper-tract urothelial carcinoma is offered by 80% and 46% of respondents,

respectively. Adjuvant chemotherapy for treatment of MIBC and upper-tract urothelial carcinoma is offered by 46% and 42% of respondents, respectively. NACT was not offered by 49%, 29%,

and 35% of respondents if Eastern Cooperative Oncology Group performance status was 3 or greater, if patients had T2 lesions without lymphovascular invasion, and if the glomerular

filtration rate was $< 50 \text{ ml/min}$, respectively. Chemotherapy regimens included

gemcitabine/cisplatin (90%), methotrexate/vinblastine/adriamycin/cisplatin (30%), dose-dense methotrexate, vinblastine, adriamycin, and cisplatin (20%), and gemcitabine/carboplatin (37%).

CONCLUSIONS: Most MedOncs (79%) in this survey offer perioperative chemotherapy to all patients with MIBC. This increased use of NACT is higher than previously reported, suggesting an increase in the adoption of recommendations that follow best evidence.

Apostolidis, P. F., & Trussell, L. O. (2014). Chemical synaptic transmission onto superficial stellate cells of the mouse dorsal cochlear nucleus. *Journal of Neurophysiology*, 111(9), 1812-1822.

The dorsal cochlear nucleus (DCN) is a cerebellum-like auditory brain stem region whose functions include sound localization and multisensory integration. Although previous in vivo studies have shown that glycinergic and GABAergic inhibition regulate the activity of several DCN cell types in response to sensory stimuli, data regarding the synaptic inputs onto DCN inhibitory interneurons remain limited. Using acute DCN slices from mice, we examined the properties of excitatory and inhibitory synapses onto the superficial stellate cell, a poorly understood cell type that provides inhibition to DCN output neurons (fusiform cells) as well as to local inhibitory interneurons (cartwheel cells). Excitatory synapses onto stellate cells activated both NMDA receptors and fast-gating, Ca²⁺-permeable AMPA receptors. Inhibition onto superficial stellate cells was mediated by glycine and GABA_A receptors with different temporal kinetics. Paired recordings revealed that superficial stellate cells make reciprocal synapses and autapses, with a connection probability of ~18-20%. Unexpectedly, superficial stellate cells co-released both glycine and GABA, suggesting that cotransmission may play a role in fine-tuning the duration of inhibitory transmission. © 2014 the American Physiological Society.

Artigas, M. L., Llebot, C., Ross, O. N., Neszi, N. Z., Rodellas, V., Garcia-Orellana, J., et al. (2014).

Understanding the spatio-temporal variability of phytoplankton biomass distribution in a microtidal mediterranean estuary. *Deep-Sea Research Part II: Topical Studies in Oceanography*, 101, 180-192.

Understanding the spatio-temporal variability of phytoplankton in aquaculture zones is necessary for the prevention and/or prediction of harmful algal bloom events. Synoptic cruises, time series analyses of physical and biological parameters, and 3D modeling were combined to investigate

the variability of phytoplankton biomass in Alfacs Bay at basin scale. This microtidal estuary located in the NW Mediterranean is an important area of shellfish and finfish exploitation, which is regularly affected by toxic outbreaks. Observations showed the existence of a preferential phytoplankton accumulation area on the NE interior of the bay. This pattern can be observed throughout the year, and we show that it is directly linked to the physical forcing in the bay, in particular, the interplay between freshwater input and wind-induced turbulence. Both drivers affect the strength of the estuarine circulation, explaining nearly 75% of the variability in phytoplankton biomass. More cells are retained when stratification is weakened and the estuarine circulation reduced, while flushing rates are higher during times of increased stratification and stronger estuarine flow. This has been confirmed by using a 3D hydrodynamic model with Eulerian tracers. Nutrients, while important to support phytoplankton populations, have been found to play only a secondary role in explaining this variability at basin scale. © 2014 Elsevier Ltd.

Aslam, M. F., Krashin, J., & Denman, M. A. (2014). Recurrent urethro-vaginal fistula following urethral injury and repair at the time of transobturator tape sling insertion. *Journal of Obstetrics and Gynaecology : The Journal of the Institute of Obstetrics and Gynaecology*, , 1-2.

Aspinwall, L. G., Taber, J. M., Kohlmann, W., Leaf, S. L., & Leachman, S. A. (2014). Unaffected family members report improvements in daily routine sun protection 2 years following melanoma genetic testing. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*,

Purpose: Reducing ultraviolet radiation exposure may decrease melanoma risk in the hereditary melanoma setting. It is unknown whether genetic counseling and test reporting of CDKN2A/p16 mutation status promote long-term compliance with photoprotection recommendations, especially in unaffected mutation carriers. Methods: This study evaluated changes 2 years following melanoma genetic testing in self-reported practice of sun protection (sunscreen, photoprotective clothing, and ultraviolet radiation avoidance) among 37 members of two CDKN2A/p16 kindreds (10 unaffected carriers, 11 affected carriers, and 16 unaffected noncarriers; response rate = 64.9% of eligible participants). Results: Multivariate profile analysis indicated that all three

participant groups reported increased daily routine practice of sun protection 2 years following melanoma genetic testing ($P < 0.02$), with 96.9% reporting that at least one sun protection behavior was part of their daily routine, up from 78.1% at baseline ($P < 0.015$). Unaffected carriers ($P < 0.024$) and unaffected noncarriers ($P < 0.027$) reported significantly more frequent use of photoprotective clothing. Affected carriers maintained adherence to all sun protection behaviors. Reported sunburns in the past 6 months decreased significantly ($P < 0.018$). Conclusion: Members of high-risk families reported increased daily routine sun protection and decreased sunburns 2 years following melanoma genetic testing, with no net decline in sun protection following negative test results. Thus, genetic testing and counseling may motivate sustained improvements in prevention behaviors. *Genet Med* advance online publication 24 April 2014 *Genetics in Medicine* (2014); doi:10.1038/gim.2014.37.

Assländer, L., & Peterka, R. J. (2014). Sensory reweighting dynamics in human postural control. *Journal of Neurophysiology*, 111(9), 1852-1864.

Healthy humans control balance during stance by using an active feedback mechanism that generates corrective torque based on a combination of movement and orientation cues from visual, vestibular, and proprioceptive systems. Previous studies found that the contribution of each of these sensory systems changes depending on perturbations applied during stance and on environmental conditions. The process of adjusting the sensory contributions to balance control is referred to as sensory reweighting. To investigate the dynamics of reweighting for the sensory modalities of vision and proprioception, 14 healthy young subjects were exposed to six different combinations of continuous visual scene and platform tilt stimuli while sway responses were recorded. Stimuli consisted of two components: 1) a pseudorandom component whose amplitude periodically switched between low and high amplitudes and 2) a low-amplitude sinusoidal component whose amplitude remained constant throughout a trial. These two stimuli were mathematically independent of one another and, thus, permitted separate analyses of sway responses to the two components. For all six stimulus combinations, the sway responses to the constant-amplitude sine were influenced by the changing amplitude of the pseudorandom component in a manner consistent with sensory reweighting. Results show clear evidence of intra- and intermodality reweighting. Reweighting dynamics were asymmetric, with slower

reweighting dynamics following a high-to-low transition in the pseudorandom stimulus amplitude compared with low-to-high amplitude shifts, and were also slower for inter- compared with intramodality reweighting. © 2014 the American Physiological Society.

Bai, X. Y., Zhang, P., Yang, Q., Liu, X. C., Wang, J., Tong, Y. L., et al. (2014). Suxiao jiuxin pill induces potent relaxation and inhibition on contraction in human artery and the mechanism. *Evidence-Based Complementary and Alternative Medicine : ECAM*, 2014, 956924.

Suxiao Jiuxin Pill, a compound Chinese traditional medicine with main components of tetramethylpyrazine and borneol, is widely used for antiangina treatment in China but its pharmacological effect on human blood vessels is unknown. We investigated the effect and possible mechanism of SJP in the human internal mammary artery (IMA, n = 78) taken from patients undergoing coronary surgery. SJP caused full relaxation in KCl- (99.4 +/- 10.5%, n = 6) and U46619- (99.9 +/- 5.6%, n = 6) contracted IMA. Pretreatment of IMA with plasma concentrations of SJP (1 mg/mL), calculated from the plasma concentration of its major component borneol, significantly depressed the maximal contraction to KCl (from 35.8 +/- 6.0 mN to 12.6 +/- 5.6 mN, P = 0.03) and U46619 (from 19.4 +/- 2.9 mN to 5.7 +/- 2.4 mN, P = 0.007) while SJP at 10 mg/mL abolished the subsequent contraction. Endothelium denudation and inhibition of eNOS significantly altered the SJP-induced relaxation without changes of eNOS expression. We conclude that SJP has a potent inhibitory effect on the vasoconstriction mediated by a variety of vasoconstrictors in human arteries. The vasorelaxation involves both endothelium-dependent and -independent mechanisms. Thus, the effect of SJP on human arteries demonstrated in this study may prove to be particularly important in vasorelaxing therapy in cardiovascular disease.

Bailey, T. S., Ahmann, A., Brazg, R., Christiansen, M., Garg, S., Watkins, E., et al. (2014). Accuracy and acceptability of the 6-day enlite continuous subcutaneous glucose sensor. *Diabetes Technology and Therapeutics*, 16(5), 277-283.

Objective: This study evaluated the performance and acceptability of the Enlite® glucose sensor (Medtronic MiniMed, Inc., Northridge, CA). Subjects and Methods: Ninety adults with type 1 or type 2 diabetes wore two Enlite sensors on the abdomen and/or buttock for 6 days and calibrated

them at different frequencies. On Days 1, 3, and 6, accuracy was evaluated by comparison of sensor glucose values with frequently sampled plasma glucose values collected over a 12-h period. Accuracy was assessed at different reference glucose concentrations and during times when absolute glucose concentration rates of change were 2 mg/dL/min. The sensor's ability to detect hypoglycemia or hyperglycemia was evaluated with simulated alerts. Subject satisfaction was evaluated with a 7-point Likert-type questionnaire, with a score of 7 indicating strong agreement. Results: With abdomen sensors under actual-use calibration (mean, 2.8 ± 0.9 times/day), the overall mean (median) absolute relative difference (ARD) values between sensor and reference values were 13.6% (10.1%); the corresponding buttock sensor ARD values were 15.5% (10.5%). With abdomen sensors under minimal calibration (mean, 1.2 ± 0.9 times/day), the mean (median) ARD values were 14.7% (10.8%). Mean ARD values of abdomen sensors at rates of change of 2 mg/dL/min were 13.6%, 12.9%, and 16.3%, respectively. With abdomen sensors, 79.5% and 94.1% of hypoglycemic and hyperglycemic events, respectively, were correctly detected; 81.9% and 94.9% of hypoglycemic and hyperglycemic alerts, respectively, were confirmed. The failure rates for abdomen and buttock sensors were 19.7% and 13.9%, respectively. Mean responses to survey questions for all subjects related to comfort and ease of use were favorable. Conclusions: The Enlite sensor provided accurate data at different glucose concentrations and rates of change. Subjects found the sensor comfortable and easy to use. © Mary Ann Liebert, Inc.

Barker, A. F., Bergeron, A., Rom, W. N., & Hertz, M. I. (2014). Obliterative bronchiolitis. *The New England Journal of Medicine*, *370*(19), 1820-1828.

Barkley-Levenson, A. M., & Crabbe, J. C. (2014). High drinking in the dark mice: A genetic model of drinking to intoxication. *Alcohol*, *48*(3), 217-223.

Drinking to intoxication is a critical component of risky drinking behaviors in humans, such as binge drinking. Previous rodent models of alcohol consumption largely failed to demonstrate that animals were patterning drinking in such a way as to experience intoxication. Therefore, few rodent models of binge-like drinking and no specifically genetic models were available to study possible predisposing genes. The High Drinking in the Dark (HDID) selective breeding project was

started to help fill this void, with HDID mice selected for reaching high blood alcohol levels in a limited access procedure. HDID mice now represent a genetic model of drinking to intoxication and can be used to help answer questions regarding predisposition toward this trait as well as potential correlated responses. They should also prove useful for the eventual development of better therapeutic strategies. © 2014 Elsevier Inc.

Barnard, D., & Yaffe, M. J. (2014). What is the physician's responsibility to a patient's family caregiver? *The Virtual Mentor : VM*, 16(5), 330-338.

Barthelme, D., Chen, J. Z., Grabenstatter, J., Baker, T. A., & Sauer, R. T. (2014). Architecture and assembly of the archaeal Cdc48-20S proteasome. *Proceedings of the National Academy of Sciences of the United States of America*, 111(17), E1687-E1694.

ATP-dependent proteases maintain protein quality control and regulate diverse intracellular functions. Proteasomes are primarily responsible for these tasks in the archaeal and eukaryotic domains of life. Even the simplest of these proteases function as large complexes, consisting of the 20S peptidase, a barrel-like structure composed of four heptameric rings, and one or two AAA+ (ATPase associated with a variety of cellular activities) ring hexamers, which use cycles of ATP binding and hydrolysis to unfold and translocate substrates into the 20S proteolytic chamber. Understanding how the AAA+ and 20S components of these enzymes interact and collaborate to execute protein degradation is important, but the highly dynamic nature of prokaryotic proteasomes has hampered structural characterization. Here, we use electron microscopy to determine the architecture of an archaeal Cdc48-20S proteasome, which we stabilized by site-specific cross-linking. This complex displays coaxial alignment of Cdc48 and 20S and is enzymatically active, demonstrating that AAA+ unfoldase wobbling with respect to 20S is not required for function. In the complex, the N-terminal domain of Cdc48, which regulates ATP hydrolysis and degradation, packs against the D1 ring of Cdc48 in a coplanar fashion, constraining mechanisms by which the N-terminal domain alters 20S affinity and degradation activity.

Bayliss, E. A., Bonds, D. E., Boyd, C. M., Davis, M. M., Finke, B., Fox, M. H., et al. (2014).

Understanding the context of health for persons with multiple chronic conditions: Moving from

what is the matter to what matters. *Annals of Family Medicine*, 12(3), 260-269.

PURPOSE An isolated focus on 1 disease at a time is insufficient to generate the scientific evidence needed to improve the health of persons living with more than 1 chronic condition. This article explores how to bring context into research efforts to improve the health of persons living with multiple chronic conditions (MCC). **METHODS** Forty-five experts, including persons with MCC, family and friend caregivers, researchers, policy makers, funders, and clinicians met to critically consider 4 aspects of incorporating context into research on MCC: key contextual factors, needed research, essential research methods for understanding important contextual factors, and necessary partnerships for catalyzing collaborative action in conducting and applying research.

RESULTS Key contextual factors involve complementary perspectives across multiple levels: public policy, community, health care systems, family, and person, as well as the cellular and molecular levels where most research currently is focused. Needed research involves moving from a disease focus toward a person-driven, goal-directed research agenda. Relevant research methods are participatory, flexible, multilevel, quantitative and qualitative, conducive to longitudinal dynamic measurement from diverse data sources, sufficiently detailed to consider what works for whom in which situation, and generative of ongoing communities of learning, living and practice. Important partnerships for collaborative action include cooperation among members of the research enterprise, health care providers, community-based support, persons with MCC and their family and friend caregivers, policy makers, and payers, including government, public health, philanthropic organizations, and the business community.

CONCLUSION Consistent attention to contextual factors is needed to enhance health research for persons with MCC. Rigorous, integrated, participatory, multimethod approaches to generate new knowledge and diverse partnerships can be used to increase the relevance of research to make health care more sustainable, safe, equitable and effective, to reduce suffering, and to improve quality of life.

Beaumont, R. H. (2014). Donald winnicott as theorist: Revolutionary or paradigm expander? *The Psychoanalytic Quarterly*, 83(2), 465-478.

Berkley, E. A., Peckham, S. D., Sampath, H., Bodewes, J., Ntambi, J. M., & Van Deelen, T. R. (2014).

Ingestion of fat tissue from wolf prey species and its influence on fatty-acid composition in sled dogs. *Wildlife Society Bulletin*, 38(1), 51-59.

We conducted feeding experiments on Canadian Inuit sled dogs (*Canis familiaris borealis*) as a surrogate for wolves (*Canis lupus*) to examine whether fatty-acid signatures could be used to estimate relative intake of common prey in the Great Lakes area, USA. We obtained fat tissue from white-tailed deer (*Odocoileus virginianus*), moose (*Alces alces*), beaver (*Castor canadensis*), and domestic cow (*Bos spp.*), and provided 8 treatments of prescribed proportions to 6-7 dogs/treatment (total 50 dogs) over a period of 60 days. Pre and post-treatment fat-tissue samples from dogs were collected by biopsy to examine fatty-acid composition. Approximately 10 60-mg samples of fat from each prey species were analyzed using gas chromatography to develop a database of fatty-acid signatures for each prey species. Fatty-acid signatures of these 4 prey species were distinct. Fatty-acid signatures of sled dogs changed with diet consistent with prescribed treatments. However, we could not reliably reconstruct their actual diet using Iverson et al.'s (2004) model. This study demonstrates that analysis of both prey and predator's fatty-acid composition may be an innovative method to estimate dietary history of a terrestrial predator, such as wolves, but additional work is needed to make dietary predictions. © 2013 The Wildlife Society.

Bernstam, E. V., Herskovic, J. R., & Hersh, W. R. (2008). *Query log analysis in biomedicine* IGI Global.

Clinicians, researchers and members of the general public are increasingly using information technology to cope with the explosion in biomedical knowledge. This chapter describes the purpose of query log analysis in the biomedical domain as well as features of the biomedical domain such as controlled vocabularies (ontologies) and existing infrastructure useful for query log analysis. We focus specifically on MEDLINE, which is the most comprehensive bibliographic database of the world's biomedical literature, the PubMed interface to MEDLINE, the Medical Subject Headings vocabulary and the Unified Medical Language System. However, the approaches discussed here can also be applied to other query logs. We conclude with a look toward the future of biomedical query log analysis. © 2009, IGI Global.

Beste, L. A., Ioannou, G. N., Yang, Y., Chang, M. F., Ross, D., & Dominitz, J. A. (2014). Improved surveillance for hepatocellular carcinoma with a primary care-oriented clinical reminder. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*,

BACKGROUND & AIMS: Surveillance of patients with cirrhosis for hepatocellular carcinoma (HCC) with liver ultrasound every 6 months has been linked with longer survival and greater use of definitive treatment. However, 1 primary care visit to 8 Veterans Affairs (VA) facilities over 18 months. Clinicians at 1 facility were sent a reminder to perform liver ultrasound assessments for patients with cirrhosis who had not received surveillance in the preceding 6 months. Outcomes included the proportion of patients receiving adequate HCC surveillance (defined as >2 instances of liver imaging >6 months apart) and HCC diagnosis and stage. As a quality improvement project, this study did not require approval by an Institutional Review Board under Federal law and VA policy. RESULTS: Baseline rates of adequate HCC surveillance were similar at all facilities (18.2% at intervention site vs 16.1% elsewhere, $P=.23$). After the reminder was implemented, adequate surveillance at the intervention site (for 790 patients) increased by 51% but was unchanged at the other facilities (for 2094 patients) (27.6% vs 17.5%, $P<.001$). Adequate surveillance occurred more often at the intervention site (adjusted odds ratio 1.29; 95% confidence interval, 1.03-1.61; $P=.02$). A higher crude percentage of patients was diagnosed with HCC at the intervention site than elsewhere (3.2% vs 1.9%; $P=.03$). We detected no difference in tumor stage at diagnosis. CONCLUSIONS: In a VA population, a clinical reminder system increased HCC surveillance in patients with cirrhosis.

Bethell, C., Gombojav, N., Carle, A., Neff, J., Newacheck, P., & Koch, T. (2014). When complex care goes complementary. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A114.

Bethell, C., Kemper, K., Gombojav, N., & Koch, T. (2014). Complementary and conventional medicine use among youth with recurrent headaches. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A30-1.

Bhayani, N. H., Kurian, A. A., Dunst, C. M., Sharata, A. M., Rieder, E., & Swanstrom, L. L. (2014). A comparative study on comprehensive, objective outcomes of laparoscopic heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. *Annals of Surgery, 259*(6), 1098-1103.

OBJECTIVE:: To compare symptomatic and objective outcomes between HM and POEM.

BACKGROUND:: The surgical gold standard for achalasia is laparoscopic Heller myotomy (HM) and partial fundoplication. Per-oral endoscopic myotomy (POEM) is a less invasive flexible endoscopic alternative. We compare their safety and efficacy. METHODS:: Data on consecutive HMs and POEMs for achalasia from 2007 to 2012 were collected. Primary outcomes: swallowing function - 1 and 6 months after surgery. Secondary outcomes: operative time, complications, postoperative gastro-esophageal reflux disease (GERD). RESULTS:: There were 101 patients: 64 HMs (42% Toupet and 58% Dor funduplications) and 37 POEMs. Presenting symptoms were comparable. Median operative time (149 vs 120 min, $P < 0.001$) and mean hospitalization (2.2 vs 1.1 days, $P < 0.0001$) were significantly higher for HMs. Postoperative morbidity was comparable. One-month Eckardt scores were significantly better for POEMs (1.8 vs 0.8, $P < 0.0001$). At 6 months, both groups had sustained similar improvements in their Eckardt scores (1.7 vs 1.2, $P = 0.1$). Both groups had significant improvements in postmyotomy lower esophageal sphincter profiles. Postmyotomy resting pressures were higher for POEMs than for HMs (16 vs 7.1 mm Hg, $P = 0.006$). Postmyotomy relaxation pressures and distal esophageal contraction amplitudes were not significantly different between groups. Routine postoperative 24-hour pH testing was obtained in 48% Hellsers and 76% POEMs. Postoperatively, 39% of POEMs and 32% of HM had abnormal acid exposure ($P = 0.7$). CONCLUSIONS:: POEM is an endoscopic therapy for achalasia with a shorter hospitalization than HM. Patient symptoms and esophageal physiology are improved equally with both procedures. Postoperative esophageal acid exposure is the same for both. The POEM is comparable with laparoscopic HM for safe and effective treatment of achalasia. © 2013 Lippincott Williams & Wilkins.

Blount, R. J., Tran, B., Jarlsberg, L. G., Phan, H., Thanh Hoang, V., Nguyen, N. V., et al. (2014). Childhood tuberculosis in northern viet nam: A review of 103 cases. *PloS One, 9*(5), e97267.

BACKGROUND: Childhood tuberculosis causes significant morbidity and mortality in Southeast Asia, yet little is known about the epidemiology and clinical characteristics of this disease in Viet

Nam. OBJECTIVES: To determine the demographics, clinical presentations, radiographic and microbiologic findings, treatment regimens, and outcomes of children admitted with tuberculosis (TB) to a national referral hospital in Viet Nam. METHODS: We conducted a retrospective case series study of children ≤ 15 years old with bacteriologically confirmed or clinically diagnosed TB admitted to a national referral hospital in Ha Noi, Viet Nam from January through December 2007. RESULTS: One hundred three children were identified: median age 5 years (IQR 2-10), 44% female, 99% Kinh ethnicity, 27% residing in Ha Noi, 88% with BCG vaccination, 27% with known TB contact, and 38% malnourished. Intrathoracic TB was present in 62%, extrathoracic in 52%, both intra and extrathoracic in 19%, and undetermined site in 5%. The most common extrathoracic manifestation was peripheral lymphadenitis, and children under 5 were more likely to have miliary TB or both intra and extrathoracic TB. Fever and failure to thrive were common presenting symptoms among all participants (65% and 56%, respectively), 66% of those with intrathoracic TB presented with cough, and 92% of those with TB meningitis presented with severe neurologic impairment. Acid-fast bacilli smears and mycobacterial cultures were positive in 18% and 21% of children tested, and histopathology was positive in 88% of those biopsied. There were no adverse drug reactions necessitating change in therapy, and no inpatient mortality. CONCLUSIONS: Extrathoracic TB was common, treatment well tolerated and clinical outcomes excellent. Culture confirmation rates were low and emphasize the need for improved diagnostics.

Bordeleau, L., Yakubovich, N., Dagenais, G. R., Rosenstock, J., Probstfield, J., Yu, P. C., et al. (2014).

The association of basal insulin glargine and/or n-3 fatty acids with incident cancers in patients with dysglycemia. *Diabetes Care*, 37(5), 1360-1366.

OBJECTIVE: Epidemiologic studies linking insulin glargine and glucose-lowering therapies to cancers and n-3 fatty acids to cancer prevention have not been confirmed. We aimed to assess the effect of insulin glargine and n-3 fatty acids on incident cancers within the context of the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial. RESEARCH DESIGN AND METHODS: The ORIGIN trial is an international, long-term, randomized two-by-two factorial study comparing insulin glargine with standard care and n-3 fatty acids with placebo (double blind) in people with dysglycemia at high risk for cardiovascular events. The primary outcome

measure (cancer substudy) was the occurrence of any new or recurrent adjudicated cancer. Cancer mortality and cancer subtypes were also analyzed. RESULTS: Among 12,537 people (mean age 63.5 years, SD 7.8; 4,388 females), 953 developed a cancer event during the median follow-up of 6.2 years. In the glargine and standard care groups, the incidence of cancers was 1.32 and 1.32 per 100 person-years, respectively ($P = 0.97$), and in the n-3 fatty acid and placebo groups, it was 1.28 and 1.36 per 100 person-years, respectively ($P = 0.39$). No difference in the effect of either intervention was noted within predefined subgroups (P for all interactions ≥ 0.17). Cancer-related mortality and cancer-specific outcomes also did not differ between groups. Postrandomization HbA1c levels, glucose-lowering therapies (including metformin), and BMI did not affect cancer outcomes. CONCLUSIONS: Insulin glargine and n-3 fatty acids have a neutral association with overall and cancer-specific outcomes, including cancer-specific mortality. Exposure to glucose-lowering therapies, including metformin, and HbA1c level during the study did not alter cancer risk. © 2014 by the American Diabetes Association.

Boudko, S. P., Ishikawa, Y., Nix, J., Chapman, M. S., & Bächinger, H. P. (2014). Structure of human peptidyl-prolyl cis-trans isomerase FKBP22 containing two EF-hand motifs. *Protein Science*, 23(1), 67-75.

The FK506-binding protein (FKBP) family consists of proteins with a variety of protein-protein interaction domains and versatile cellular functions. It is assumed that all members are peptidyl-prolyl cis-trans isomerases with the enzymatic function attributed to the FKBP domain. Six members of this family localize to the mammalian endoplasmic reticulum (ER). Four of them, FKBP22 (encoded by the FKBP14 gene), FKBP23 (FKBP7), FKBP60 (FKBP9), and FKBP65 (FKBP10), are unique among all FKBP family members as they contain the EF-hand motifs. Little is known about the biological roles of these proteins, but emerging genetics studies are attracting great interest to the ER resident FKBP family members, as mutations in genes encoding FKBP10 and FKBP14 were shown to cause a variety of matrix disorders. Although the structural organization of the FKBP-type domain as well as of the EF-hand motif has been known for a while, it is difficult to conclude how these structures are combined and how it affects the protein functionality. We have determined a unique 1.9 Å resolution crystal structure for human FKBP22, which can serve as a prototype for other EF hand-containing FKBP family members. The EF-hand motifs of two FKBP22 molecules form a dimeric

complex with an elongated and predominantly hydrophobic cavity that can potentially be occupied by an aliphatic ligand. The FKBP-type domains are separated by a cleft and their putative active sites can catalyze isomerization of two bonds within a polypeptide chain in extended conformation. These structural results are of prime interest for understanding biological functions of ER resident FKBP containing EF-hand motifs. © 2013 The Protein Society.

Boyle, E. A., O'Roak, B. J., Martin, B. K., Kumar, A., & Shendure, J. (2014). MIPgen: Optimized modeling and design of molecular inversion probes for targeted resequencing. *Bioinformatics (Oxford, England)*,

SUMMARY: Molecular Inversion Probes (MIPs) enable cost-effective multiplex targeted gene resequencing in very large cohorts. However, the design of individual MIPs is a critical parameter governing the performance of this technology with respect to capture uniformity and specificity. MIPgen is a user-friendly package that simplifies the process of designing custom Molecular Inversion Probe assays to arbitrary targets. New logistic and SVM-derived models enable in silico predictions of assay success, and a redesigned assay exhibits improved coverage uniformity relative to previous methods, which in turn improves the utility of MIPs for cost-effective targeted sequencing for candidate gene validation and for diagnostic sequencing in a clinical setting. Availability and Implementation: MIPgen is implemented in C++. Source code and accompanying Python scripts are available at <http://krishna.gs.washington.edu/download/mipgen> with the username "download". CONTACT: shendure@uw.edu and boylee@uw.edu.

Braun, J., Baraliakos, X., Hermann, K. - . A., Deodhar, A., Van Der Heijde, D., Inman, R., et al. (2014).

The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: Results through 4 years of the GO-RAISE trial. *Annals of the Rheumatic Diseases*, 73(6), 1107-1113.

Objective To evaluate radiographic progression in patients with ankylosing spondylitis (AS) receiving two different doses of the tumour necrosis factor antagonist golimumab. Methods: 356 patients with AS were randomly assigned to placebo, or golimumab 50 mg or 100 mg every 4 weeks (wks). At wk16, patients with inadequate response early escaped with blinded dose adjustments (placebo→golimumab 50 mg, 50 mg→100 mg). At wk24, patients still receiving placebo crossed over to golimumab 50 mg. Lateral view radiographs of the cervical/lumbar spine

were obtained at wk0, wk104 and wk208, and scored (two blinded readers, modified Stoke AS Spine Score (mSASSS)). Observed data were used for wk104 analyses; missing wk208 scores were linearly extrapolated. Results: Wk104 changes from baseline in mSASSS averaged 1.6 ± 4.6 for placebo crossover, 0.9 ± 2.7 for 50 mg and 0.9 ± 3.9 for 100 mg. By wk208, following golimumab therapy for 3.5-4 years, mean changes in mSASSS were 2.1 ± 5.2 for placebo crossover, 1.3 ± 4.1 for 50 mg and 2.0 ± 5.6 for 100 mg. Less than a third of patients (placebo crossover, 19/66 (28.8%); 50 mg, 29/111 (26.1%); 100 mg, 35/122 (28.7%)) had a definitive change from baseline mSASSS (>2). Less radiographic progression was observed through wk208 in patients without baseline syndesmophytes (0.2 vs 2.8 in patients with ≥ 1 syndesmophyte; $p=0.0004$). Conclusions: No difference in mSASSS change was observed between golimumab 50 mg and 100 mg. The radiographic progression rate remained stable at years 2 and 4, suggesting no acceleration of new bone formation over time. Golimumab-treated AS patients with no syndesmophytes and less systemic inflammation at baseline had considerably less radiographic progression.

Burke, B. J., Anderson, J. J., & Baptista, A. M. (2014). Evidence for multiple navigational sensory capabilities of chinook salmon. *Aquatic Biology*, 20(1), 77-90.

To study the complex coastal migrations patterns exhibited by juvenile Columbia River Chinook salmon as they enter and move through the marine environment, we created an individual-based model in a coupled Eulerian-Lagrangian framework. We modeled 5 distinct migration strategies and compared the resulting spatial distributions to catch data collected during May and June in 3 years. Two strategies produced fish distributions similar to those observed in May, but only one also produced the observed June distributions. In both strategies, salmon distinguish north from south (i.e. they have a compass sense), and they control their position relative to particular landmarks, such as the river mouth. With these 2 abilities, we posit that salmon follow spatially explicit behavior rules that prevent entrapment in strong southward currents and advection offshore. Additionally, the consistent spatio-temporal distributions observed among years suggest that salmon use a clock sense to adjust their swim speed, within and among years, in response to progress along their migration. © The authors 2014.

Burwitz, B. J., Reed, J. S., Hammond, K. B., Ohme, M. A., Planer, S. L., Legasse, A. W., et al. (2014).

Technical advance: Liposomal alendronate depletes monocytes and macrophages in the nonhuman primate model of human disease. *Journal of Leukocyte Biology*,
Nonhuman primates are critical animal models for the study of human disorders and disease and offer a platform to assess the role of immune cells in pathogenesis via depletion of specific cellular subsets. However, this model is currently hindered by the lack of reagents that safely and specifically ablate myeloid cells of the monocyte/macrophage Lin. Given the central importance of macrophages in homeostasis and host immunity, development of a macrophage-depletion technique in nonhuman primates would open new avenues of research. Here, using LA at i.v. doses as low as 0.1 mg/kg, we show a >50% transient depletion of circulating monocytes and tissue-resident macrophages in RMs by an 11-color flow cytometric analysis. Diminution of monocytes was followed rapidly by emigration of monocytes from the bone marrow, leading to a rebound of monocytes to baseline levels. Importantly, LA was well-tolerated, as no adverse effects or changes in gross organ function were observed during depletion. These results advance the ex vivo study of myeloid cells by flow cytometry and pave the way for in vivo studies of monocyte/macrophage biology in nonhuman primate models of human disease.

Bush, N. E., Dobscha, S. K., Crumpton, R., Denneson, L. M., Hoffman, J. E., Crain, A., et al. (2014). A

virtual hope box smartphone app as an accessory to therapy: Proof-of-concept in a clinical sample of veterans. *Suicide and Life-Threatening Behavior*,

A "Hope Box" is a therapeutic tool employed by clinicians with patients who are having difficulty coping with negative thoughts and stress, including patients who may be at risk of suicide or nonsuicidal self-harm. We conducted a proof-of-concept test of a "Virtual" Hope Box (VHB)-a smartphone app that delivers patient-tailored coping tools. Compared with a conventional hope box integrated into VA behavioral health treatment, high-risk patients and their clinicians used the VHB more regularly and found the VHB beneficial, useful, easy to set up, and said they were likely to use the VHB in the future and recommend the VHB to peers. © 2014.

C Ang, D., Warrick, A. L., Shilling, A., Beadling, C., Corless, C. L., & Troxell, M. L. (2014). Frequent phosphatidylinositol-3-kinase mutations in proliferative breast lesions. *Modern Pathology*, 27(5),

740-750.

The phosphatidylinositol-3-kinase pathway is one of the most commonly altered molecular pathways in invasive breast carcinoma, with phosphatidylinositol-3-kinase catalytic subunit (PIK3CA) mutations in 25% of invasive carcinomas. Ductal carcinoma in situ (DCIS), benign papillomas, and small numbers of columnar cell lesions harbor an analogous spectrum of PIK3CA and AKT1 mutations, yet there is little data on usual ductal hyperplasia and atypical ductal and lobular neoplasias. We screened 192 formalin-fixed paraffin-embedded breast lesions from 75 patients for point mutations using a multiplexed panel encompassing 643 point mutations across 53 genes, including 58 PIK3CA substitutions. PIK3CA point mutations were identified in 31/62 (50%) proliferative lesions (usual ductal hyperplasia and columnar cell change), 10/14 (71%) atypical hyperplasias (atypical ductal hyperplasia and flat epithelial atypia), 7/16 (44%) lobular neoplasias (atypical lobular hyperplasia and lobular carcinoma in situ), 10/21 (48%) DCIS, and 13/37 (35%) invasive carcinomas. In genotyping multiple lesions of different stage from the same patient/specimen, we found considerable heterogeneity; most notably, in 12 specimens the proliferative lesion was PIK3CA mutant but the concurrent carcinoma was wild type. In 11 additional specimens, proliferative epithelium and cancer contained different point mutations. The frequently discordant genotypes of usual ductal hyperplasia/columnar cell change and concurrent carcinoma support a role for PIK3CA-activating point mutations in breast epithelial proliferation, perhaps more so than transformation. Further, these data suggest that proliferative breast lesions are heterogeneous and may represent non-obligate precursors of invasive carcinoma. © 2014 USCAP, Inc.

Camargo Jr., C. A., Budinger, G. R. S., Escobar, G. J., Hansel, N. N., Hanson, C. K., Huffnagle, G. B., et al. (2014). Promotion of lung health: NHLBI workshop on the primary prevention of chronic lung diseases. *Annals of the American Thoracic Society*, 11(SUPPL. 3), S125-S138.

Lung-related research primarily focuses on the etiology and management of diseases. In recent years, interest in primary prevention has grown. However, primary prevention also includes "health promotion" (actions in a population that keep an individual healthy). We encourage more research on population-based (public health) strategies that could not only maximize lung health but also mitigate "normal" age-related declines - not only for spirometry but across multiple

measures of lung health. In developing a successful strategy, a "life course" approach is important. Unfortunately, we are unable to achieve the full benefit of this approach until we have better measures of lung health and an improved understanding of the normal trajectory, both over an individual's life span and possibly across generations. We discuss key questions in lung health promotion, with an emphasis on the upper (healthier) end of the distribution of lung functioning and resiliency and briefly summarize the few interventions that have been studied to date. We conclude with suggestions regarding the most promising future research for this important, but largely neglected, area of lung research. Copyright © 2014 by the American Thoracic Society.

Cameron, M. H., Fitzpatrick, M., Overs, S., Murchison, C., Manning, J., & Whitham, R. (2014).

Dalfampridine improves walking speed, walking endurance, and community participation in veterans with multiple sclerosis: A longitudinal cohort study. *Multiple Sclerosis, 20*(6), 733-738.

Background: In short-term trials, dalfampridine extended release (ER) improves walking in people with multiple sclerosis (MS). The tolerability and effects of dalfampridine-ER in clinical practice have not been reported. Objectives: The objective of this paper is to determine the clinical tolerability and effects of dalfampridine on walking and community participation. Methods: All patients at the Portland VA Medical Center prescribed dalfampridine-ER over one year completed the Timed 25-Foot Walk (T25FW), Multiple Sclerosis Walking Scale-12 (MSWS-12), Two-Minute Timed Walk (2MTW), and Community Integration Questionnaire (CIQ) at baseline and follow-up clinic visits. Ongoing use and measures over one year were analyzed. Results: A total of 39 patients (mean age 56.5 years, mean disease duration 19.5 years, 82% male, 38% relapsing-remitting MS, 62% progressive MS) were prescribed dalfampridine-ER. Twenty-four (62%) continued to take dalfampridine-ER. At initial follow-up, all measures improved significantly from baseline (T25FW: -2.7 s, $p = 0.004$; 2MTW: 41 feet (ft), $p = 0.002$; MSWS-12: -11, $p < 0.001$; CIQ: 1.2, $p = 0.003$). At one year, walking endurance and self-perceived walking were still significantly improved (2MTW: 33 ft, $p = 0.03$; MSWS-12: 5.9, $p = 0.007$). Conclusions: Dalfampridine-ER was associated with short-term improvements in walking speed and community participation, and sustained improvements in walking endurance and self-

perceived impact of MS on walking for one year. Our study supports the utility of this medication in late MS. © The Author(s) 2013.

Carney, N., Ghajar, J., Jagoda, A., Bedrick, S., Davis-O'Reilly, C., du Coudray, H., et al. (2014).

Executive summary: Concussion guidelines step 1: Systematic review of prevalent indicators. *Neurosurgery*,

Chenevert, T. L., Malyarenko, D. I., Newitt, D., Li, X., Jayatilake, M., Tudorica, A., et al. (2014). Errors in quantitative image analysis due to platform-dependent image scaling. *Translational Oncology*, 7(1), 65-71.

PURPOSE: To evaluate the ability of various software (SW) tools used for quantitative image analysis to properly account for source-specific image scaling employed by magnetic resonance imaging manufacturers. METHODS: A series of gadoteridol-doped distilled water solutions (0%, 0.5%, 1%, and 2% volume concentrations) was prepared for manual substitution into one (of three) phantom compartments to create "variable signal," whereas the other two compartments (containing mineral oil and 0.25% gadoteriol) were held unchanged. Pseudodynamic images were acquired over multiple series using four scanners such that the histogram of pixel intensities varied enough to provoke variable image scaling from series to series. Additional diffusion-weighted images were acquired of an ice-water phantom to generate scanner-specific apparent diffusion coefficient (ADC) maps. The resulting pseudodynamic images and ADC maps were analyzed by eight centers of the Quantitative Imaging Network using 16 different SW tools to measure compartment-specific region-of-interest intensity. RESULTS: Images generated by one of the scanners appeared to have additional intensity scaling that was not accounted for by the majority of tested quantitative image analysis SW tools. Incorrect image scaling leads to intensity measurement bias near 100%, compared to nonscaled images. CONCLUSION: Corrective actions for image scaling are suggested for manufacturers and quantitative imaging community.

Cheng, Y. W., Shaffer, B. L., Nicholson, J. M., & Caughey, A. B. (2014). In reply. *Obstetrics and Gynecology*, 123(6), 1360.

Cheng, Y. W., Shaffer, B. L., Nicholson, J. M., & Caughey, A. B. (2014). In reply. *Obstetrics and Gynecology*, 123(6), 1359.

Cheng, Y. W., Snowden, J. M., Caughey, A. B., & King, T. L. (2014). Reply. *American Journal of Obstetrics and Gynecology*, 210(5), 489-490.

Chennupati, S. K., Pelizzari, C. A., Kunnavakkam, R., & Liauw, S. L. (2014). Late toxicity and quality of life after definitive treatment of prostate cancer: Redefining optimal rectal sparing constraints for intensity-modulated radiation therapy. *Cancer Medicine*,

The objective of this study was to assess late toxicity and quality of life (QOL) for patients receiving definitive intensity-modulated radiotherapy (IMRT) and image-guided radiation therapy (IGRT) with regard to normal tissue sparing objectives. Three hundred and seventy-two consecutive men treated with definitive IMRT for prostate adenocarcinoma. Toxicity was graded by CTC v3.0 genitourinary (GU) and gastrointestinal (GI) toxicity at each follow-up visit. Patient-reported QOL (EPIC-26) was prospectively collected for a subset of men. Dosimetric data for bladder and rectum were compared to toxicity and QOL global domain scores, specifically analyzing outcomes for men who met ideal rectal constraints (V70 <10%, V65 <20%, V40 <40%). The median age and prescription dose was 69 years and 76 Gy, respectively. Median follow-up was 47 months. At 4 years, freedom from Grade 2 (FFG2) GI toxicity was 92% and FFG2 GU toxicity was 76%. On univariate analysis, current smoking, larger bladder volume, and higher RT dose were associated with decreased FFG2 GU toxicity, while use of anticoagulation, increasing age, and not meeting ideal rectal constraints were associated with decreased FFG2 GI toxicity (all $P \leq 0.05$). Bowel QOL remained stable over the 2-year follow-up period and was higher for patients who met ideal rectal constraints ($P = 0.05$). IMRT with IGRT is associated with low rates of severe toxicity and a high GI and GU QOL. The use of strict rectal constraints can further improve GI QOL and reduce GI toxicity.

Chinnery, P. F., Craven, L., Mitalipov, S., Stewart, J. B., Herbert, M., & Turnbull, D. M. (2014). The challenges of mitochondrial replacement. *PLoS Genetics*, 10(4), e1004315.

Cho, H. H., Cargnin, F., Kim, Y., Lee, B., Kwon, R. J., Nam, H., et al. (2014). Isl1 directly controls a cholinergic neuronal identity in the developing forebrain and spinal cord by forming cell type-specific complexes. *PLoS Genetics*, 10(4), e1004280.

The establishment of correct neurotransmitter characteristics is an essential step of neuronal fate specification in CNS development. However, very little is known about how a battery of genes involved in the determination of a specific type of chemical-driven neurotransmission is coordinately regulated during vertebrate development. Here, we investigated the gene regulatory networks that specify the cholinergic neuronal fates in the spinal cord and forebrain, specifically, spinal motor neurons (MNs) and forebrain cholinergic neurons (FCNs). Conditional inactivation of Isl1, a LIM homeodomain factor expressed in both differentiating MNs and FCNs, led to a drastic loss of cholinergic neurons in the developing spinal cord and forebrain. We found that Isl1 forms two related, but distinct types of complexes, the Isl1-Lhx3-hexamer in MNs and the Isl1-Lhx8-hexamer in FCNs. Interestingly, our genome-wide ChIP-seq analysis revealed that the Isl1-Lhx3-hexamer binds to a suite of cholinergic pathway genes encoding the core constituents of the cholinergic neurotransmission system, such as acetylcholine synthesizing enzymes and transporters. Consistently, the Isl1-Lhx3-hexamer directly coordinated upregulation of cholinergic pathway genes in embryonic spinal cord. Similarly, in the developing forebrain, the Isl1-Lhx8-hexamer was recruited to the cholinergic gene battery and promoted cholinergic gene expression. Furthermore, the expression of the Isl1-Lhx8-complex enabled the acquisition of cholinergic fate in embryonic stem cell-derived neurons. Together, our studies show a shared molecular mechanism that determines the cholinergic neuronal fate in the spinal cord and forebrain, and uncover an important gene regulatory mechanism that directs a specific neurotransmitter identity in vertebrate CNS development.

Choudhury, N., Chen, F., Zha, D., Fridberger, A., Zheng, J., Jacques, S. L., et al. (2012). In vivo measurement of amplifying motion within the organ of Corti under sound stimulation using optical coherence tomography. *Optical Coherence Tomography and Coherence Domain Optical Methods in Biomedicine XVI*, San Francisco, CA. , 8213.

Hearing in mammals, depend on an amplifying motion which hypothetically uses force from outer hair cells (OHC) motility to enhance sound induced vibration of the organ of Corti of cochlea. In

this hypothesis the differential motion among key structures in this organ and the timing of the OHC force generation is essential for cochlear amplification to occur. Using a time domain optical coherence tomography system which allows us to make vibration measurements we were able to measure differential motion of two functionally important surfaces, namely, basilar membrane and reticular lamina. The reticular lamina vibrates at higher amplitude than the basilar membrane and has significant phase lead over basilar membrane vibration. The differential motion, that is, different amplitude and phase of vibration, become less as the energy of the sound stimulus is increased and the amplification processes in the organ of Corti are quenched. © 2012 SPIE.

Cleary, D. R., Roeder, Z., Elkhatib, R., & Heinricher, M. M. (2014). Neuropeptide Y in the rostral ventromedial medulla reverses inflammatory and nerve injury hyperalgesia in rats via non-selective excitation of local neurons. *Neuroscience*, 271, 149-159.

Chronic pain reflects not only sensitization of the ascending nociceptive pathways, but also changes in descending modulation. The rostral ventromedial medulla (RVM) is a key structure in a well-studied descending pathway, and contains two classes of modulatory neurons, the ON-cells and the OFF-cells. Disinhibition of OFF-cells depresses nociception; increased ON-cell activity facilitates nociception. Multiple lines of evidence show that sensitization of ON-cells contributes to chronic pain, and reversing or blocking this sensitization is of interest as a treatment of persistent pain. Neuropeptide Y (NPY) acting via the Y1 receptor has been shown to attenuate hypersensitivity in nerve-injured animals without affecting normal nociception when microinjected into the RVM, but the neural basis for this effect was unknown. We hypothesized that behavioral anti-hyperalgesia was due to selective inhibition of ON-cells by NPY at the Y1 receptor. To explore the possibility of Y1 selectivity on ON-cells, we stained for the NPY-Y1 receptor in the RVM, and found it broadly expressed on both serotonergic and non-serotonergic neurons. In subsequent behavioral experiments, NPY microinjected into the RVM in lightly anesthetized animals reversed signs of mechanical hyperalgesia following either nerve injury or chronic hindpaw inflammation. Unexpectedly, rather than decreasing ON-cell activity, NPY increased spontaneous activity of both ON- and OFF-cells without altering noxious-evoked changes in firing. Based on these results, we conclude that the anti-hyperalgesic effects of NPY in the RVM are not explained by selective inhibition of ON-cells, but rather by increased spontaneous activity of OFF-cells. Although ON-

cells undoubtedly facilitate nociception and contribute to hypersensitivity, the present results highlight the importance of parallel OFF-cell-mediated descending inhibition in limiting the expression of chronic pain. © 2014 IBRO.

Coleman, D. J., Garcia, G., Hyter, S., Jang, H. S., Chagani, S., Liang, X., et al. (2014). Retinoid-X-receptors (alpha/beta) in melanocytes modulate innate immune responses and differentially regulate cell survival following UV irradiation. *PLoS Genetics*, *10*(5), e1004321.

Understanding the molecular mechanisms of ultraviolet (UV) induced melanoma formation is becoming crucial with more reported cases each year. Expression of type II nuclear receptor Retinoid-X-Receptor alpha (RXRalpha) is lost during melanoma progression in humans. Here, we observed that in mice with melanocyte-specific ablation of RXRalpha and RXRbeta, melanocytes attract fewer IFN-gamma secreting immune cells than in wild-type mice following acute UVR exposure, via altered expression of several chemoattractive and chemorepulsive chemokines/cytokines. Reduced IFN-gamma in the microenvironment alters UVR-induced apoptosis, and due to this, the survival of surrounding dermal fibroblasts is significantly decreased in mice lacking RXRalpha/beta. Interestingly, post-UVR survival of the melanocytes themselves is enhanced in the absence of RXRalpha/beta. Loss of RXRs alpha/beta specifically in the melanocytes results in an endogenous shift in homeostasis of pro- and anti-apoptotic genes in these cells and enhances their survival compared to the wild type melanocytes. Therefore, RXRs modulate post-UVR survival of dermal fibroblasts in a "non-cell autonomous" manner, underscoring their role in immune surveillance, while independently mediating post-UVR melanocyte survival in a "cell autonomous" manner. Our results emphasize a novel immunomodulatory role of melanocytes in controlling survival of neighboring cell types besides controlling their own, and identifies RXRs as potential targets for therapy against UV induced melanoma.

Connelly, K. J., & Lafranchi, S. H. (2014). Detection of neonates with mild congenital hypothyroidism (primary) or isolated hyperthyrotropinemia: An increasingly common management dilemma. *Expert Review of Endocrinology and Metabolism*, *9*(3), 263-271.

Anywhere from 10% to 40% of neonates detected by newborn screening programs have mild

congenital hypothyroidism (thyroid-stimulating hormone [TSH] 6 to 20 mU/l with borderline low free T4) or isolated hyperthyrotropinemia. The increasing frequency of such cases appears to be chiefly the result of lowering screening TSH cutoffs. In some cases, the etiology is a mild form of dysgenesis or dysmorphogenesis; most cases, however, on imaging have gland in situ of unexplained etiology. Re-evaluation after age 3 years shows some with transient hypothyroidism, a minority with permanent hypothyroidism, while the majority have persistent, mild TSH elevation and normal free T4. There is limited data on neurodevelopmental outcome to guide management. In cases where the TSH is trending down and free T4 is normal, we recommend re-checking serum TSH and free T4 at weekly intervals. If serum TSH does not normalize by 4 weeks of age, we recommend treatment, with re-evaluation after age 2-3 years. © 2014 Informa UK, Ltd.

Corrales-Aguilar, E., Trilling, M., Hunold, K., Fiedler, M., Le, V. T., Reinhard, H., et al. (2014). Human cytomegalovirus fcgamma binding proteins gp34 and gp68 antagonize fcgamma receptors I, II and III. *PLoS Pathogens*, 10(5), e1004131.

Human cytomegalovirus (HCMV) establishes lifelong infection with recurrent episodes of virus production and shedding despite the presence of adaptive immunological memory responses including HCMV immune immunoglobulin G (IgG). Very little is known how HCMV evades from humoral and cellular IgG-dependent immune responses, the latter being executed by cells expressing surface receptors for the Fc domain of IgG (FcgammaRs). Remarkably, HCMV expresses the RL11-encoded gp34 and UL119-118-encoded gp68 type I transmembrane glycoproteins which bind Fcgamma with nanomolar affinity. Using a newly developed FcgammaR activation assay, we tested if the HCMV-encoded Fcgamma binding proteins (HCMV FcgammaRs) interfere with individual host FcgammaRs. In absence of gp34 or/and gp68, HCMV elicited a much stronger activation of FcgammaRIIIA/CD16, FcgammaRIIA/CD32A and FcgammaRI/CD64 by polyclonal HCMV-immune IgG as compared to wildtype HCMV. gp34 and gp68 co-expression culminates in the late phase of HCMV replication coinciding with the emergence of surface HCMV antigens triggering FcgammaRIII/CD16 responses by polyclonal HCMV-immune IgG. The gp34- and gp68-dependent inhibition of HCMV immune IgG was fully reproduced when testing the activation of primary human NK cells. Their broad antagonistic function towards FcgammaRIIIA,

FcγRIIA and FcγRI activation was also recapitulated in a gain-of-function approach based on humanized monoclonal antibodies (trastuzumab, rituximab) and isotypes of different IgG subclasses. Surface immune-precipitation showed that both HCMV-encoded Fcγ binding proteins have the capacity to bind trastuzumab antibody-HER2 antigen complexes demonstrating simultaneous linkage of immune IgG with antigen and the HCMV inhibitors on the plasma membrane. Our studies reveal a novel strategy by which viral FcγRs can compete for immune complexes against various Fc receptors on immune cells, dampening their activation and antiviral immunity.

Costantino, G., Casazza, G., Reed, M., Bossi, I., Sun, B., Del Rosso, A., et al. (2014). Syncope risk stratification tools vs clinical judgment: An individual patient data meta-analysis. *The American Journal of Medicine*,

BACKGROUND: there have been several attempts to derive syncope prediction tools to guide clinician decision-making. However they have not been largely adopted possibly because of their lack of sensitivity and specificity. We sought to externally validate the existing tools and to compare them to clinical judgment, using an individual patient data meta-analysis approach.

METHODS: electronic databases, bibliographies and experts in the field were screened to find all prospective studies enrolling consecutive subjects presenting with syncope to the emergency department. Prediction tools and clinical judgment were applied to all patients in each dataset. Serious outcomes and death were separately considered during emergency department stay and at 10 and 30 days after presenting syncope. Pooled sensitivities, specificities, likelihood ratios and diagnostic odds ratios, with 95% CIs were calculated. **RESULTS:** thirteen potentially relevant papers were retrieved (11 authors). Six authors agreed to share individual patient data. In total, 3681 patients were included. Three prediction tools (OESIL, SFSR, EGSYS) could be assessed by the available datasets. None of the evaluated prediction tools performed better than clinical judgment in identifying serious outcomes during emergency department stay, at 10 and 30 days after syncope. **CONCLUSIONS:** despite the use of a individual patient data approach to reduce heterogeneity between studies, a large variability was still present. Current prediction tools did not show better sensitivity, specificity, or prognostic yield compared to clinical judgment in

predicting short-term serious outcome after syncope. Our systematic review strengthens the evidence that current prediction tools should not be strictly used in clinical practice.

Cramer, S. K., Skalet, A., Mansoor, A., Wilson, D. J., & Ng, J. D. (2014). Inflammatory myofibroblastic tumor of the orbit: A case report. *Ophthalmic Plastic and Reconstructive Surgery*,
Inflammatory myofibroblastic tumor (IMT) is a neoplasm most commonly found in the abdominal-pelvic region, lung, and retroperitoneum. The tumor tends to affect soft tissues of children and young adults and can locally recur but rarely metastasizes. Histologically, the appearance is one of bland spindle cell proliferation with a prominent, chronic inflammatory infiltrate. This article describes 1 case of IMT found in the orbit that is presented with rapidly progressive painless proptosis. In the authors' review of the literature, they have only found 2 other case reports involving the orbit.

Daniels, A. H., Depasse, J. M., Magill, S. T., Fischer, S. A., Palumbo, M. A., Ames, C. P., et al. (2014).

The current state of united states spine surgery training: A survey of residency and spine fellowship program directors. *Spine Deformity*, 2(3), 176-185.

Study Design Program director survey. Objectives To collect data on spine surgical experience during orthopedic and neurological surgery residency and assess the opinions of program directors (PDs) from orthopedic and neurological surgery residencies and spine surgery fellowships regarding current spine surgical training in the United States. Summary of Background Data Current training for spine surgeons in the United States consists of a residency in either orthopedic or neurological surgery followed by an optional spine surgery fellowship. Program director survey data may assist in efforts to improve contemporary spine training. Methods An anonymous questionnaire was distributed to all PDs of orthopedic and neurological surgery residencies and spine fellowships in the United States (N = 382). A 5-point Likert scale was used to assess attitudinal questions. A 2-tailed independent-samples t test was used to compare responses to each question independently. Results A total of 147 PDs completed the survey. Orthopedic PDs most commonly indicated that their residents participate in 76 to 150 spine cases during residency, whereas neurological surgery PDs most often reported more than 450 spine cases during residency (p <.0001). Over 88% of orthopedic surgery program directors

and 0% of neurological surgery PDs recommended that their trainees complete a fellowship if they wish to perform community spine surgery ($p < .001$). In contrast, 98.1% of orthopedic PDs and 86.4% of neurological surgery PDs recommended that their trainees complete a fellowship if they wish to perform spinal deformity surgery ($p = .038$). Most PDs agreed that surgical simulation and competency-based training could improve spine surgery training (76% and 72%, respectively). Conclusions This study examined the opinions of orthopedic and neurological surgery residency and spine fellowship PDs regarding current spine surgery training in the United States. A large majority of PDs thought that both orthopedic and neurological surgical trainees should complete a fellowship if they plan to perform spinal deformity surgery. These results provide a background for further efforts to optimize contemporary spine surgical training. © 2014 Scoliosis Research Society.

Darney, B. G., Simancas-Mendoza, W., Edelman, A. B., Guerra-Palacio, C., Tolosa, J. E., & Rodriguez, M. I. (2014). Post-abortion and induced abortion services in two public hospitals in Colombia. *Contraception*,

OBJECTIVE: Until 2006, legal induced abortion was completely banned in Colombia. Few facilities are equipped or willing to offer abortion services; often adolescents experience even greater barriers of access in this context. We examined post abortion care (PAC) and legal induced abortion in two large public hospitals. We tested the association of hospital site, procedure type (manual vacuum aspiration vs. sharp curettage), and age (adolescents vs. women 20 years and over) with service type (PAC or legal induced abortion). STUDY DESIGN: Retrospective cohort study using 2010 billing data routinely collected for reimbursement (N=1353 procedures). We utilized descriptive statistics, multivariable logistic regression and predicted probabilities.

RESULTS: Adolescents made up 22% of the overall sample (300/1353). Manual vacuum aspiration was used in one-third of cases (vs. sharp curettage). Adolescents had lower odds of documented PAC (vs. induced abortion) compared with women over age 20 (OR=0.42; 95% CI=0.21-0.86). The absolute difference of service type by age, however, is very small, controlling for hospital site and procedure type (.97 probability of PAC for adolescents compared with .99 for women 20 and over). Regardless of age, PAC via sharp curettage is the current standard in these two public hospitals. CONCLUSION: Both adolescents and women over 20 are in need of access

to legal abortion services utilizing modern technologies in the public sector in Colombia.

Documentation of abortion care is an essential first step to determining barriers to access and opportunities for quality improvement and better health outcomes for women. IMPLICATIONS:

Following partial decriminalization of abortion in Colombia, in public hospitals nearly all abortion services are post-abortion care, not induced abortion. Sharp curettage is the dominant treatment for both adolescents and women over 20. Women seek care in the public sector for abortion, and must have access to safe, quality services.

Davidson, B. P., Chadderdon, S. M., Belcik, J. T., Gupta, S., & Lindner, J. R. (2014). Ischemic memory imaging in nonhuman primates with echocardiographic molecular imaging of selectin expression. *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography*,

BACKGROUND: Selectins are adhesion molecules that are expressed by the vascular endothelium upon activation and may be an imaging target for detecting myocardial ischemia long after resolution. The aim of this study was to test the hypothesis that molecular imaging of selectins with myocardial contrast echocardiographic (MCE) molecular imaging could be used to detect recent brief ischemia in closed-chest nonhuman primates. METHODS: Myocardial ischemia was produced in anesthetized adult rhesus macaques (n = 6) by percutaneous balloon catheter occlusion of the left anterior descending or circumflex coronary artery for 5 to 10 min. Three separate macaques served as nonischemic controls. MCE perfusion imaging was performed during coronary occlusion to measure risk area and at 100 to 110 min to exclude infarction. MCE molecular imaging was performed at 30 and 90 min after reperfusion using a lipid microbubble bearing dimeric recombinant human P-selectin glycoprotein ligand-1 (MB-YSPSL). Collection of blood for safety data, electrocardiography, and echocardiography were performed at baseline and before and 10 min after each MB-YSPSL injection. RESULTS: Vital signs, oxygen saturation, electrocardiographic results, ventricular systolic function, pulmonary vascular resistance, and serum safety markers were unchanged by intravenous injection of MB-YSPSL. On echocardiography, left ventricular dysfunction in the risk area had resolved by 30 min, and there was no evidence of infarction on MCE perfusion imaging. On selectin-targeted MCE molecular imaging, signal enhancement was greater ($P < .05$) in the risk area than remote territory at 30

min (25 +/- 11 vs 11 +/- 4 IU) and 90 min (13 +/- 3 vs 3 +/- 2 IU) after ischemia. There was no enhancement (<1 IU) in control nonischemic subjects. CONCLUSIONS: In primates, MCE molecular imaging of selectins using MB-YSPSL, a recombinant ligand appropriate for humans, is both safe and effective for imaging recent myocardial ischemia. This technique may be useful for detecting recent ischemia in patients with chest pain even in the absence of necrosis.

Davis, M. M., Aromaa, S., McGinnis, P. B., Ramsey, K., Rollins, N., Smith, J., et al. (2014). Engaging the underserved: A process model to mobilize rural community health coalitions as partners in translational research. *Clinical and Translational Science*,

PURPOSE: Community engagement (CE) and community-engaged research (CEnR) are increasingly recognized as critical elements in research translation. Process models to develop CEnR partnerships in rural and underserved communities are needed. METHOD: Academic partners transformed four established Community Health Improvement Partnerships (CHIPs) into Community Health Improvement and Research Partnerships (CHIRPs). The intervention consisted of three elements: an academic-community kickoff/orientation meeting, delivery of eight research training modules to CHIRP members, and local community-based participatory research (CBPR) pilot studies addressing childhood obesity. We conducted a mixed methods analysis of pre-/postsurveys, interviews, session evaluations, observational field notes, and attendance logs to evaluate intervention effectiveness and acceptability. RESULTS: Forty-nine community members participated; most (78.7%) attended five or more research training sessions. Session quality and usefulness was high. Community members reported significant increases in their confidence for participating in all phases of research (e.g., formulating research questions, selecting research methods, writing manuscripts). All CHIRP groups successfully conducted CBPR pilot studies. CONCLUSIONS: The CHIRP process builds on existing infrastructure in academic and community settings to foster CEnR. Brief research training and pilot studies around community-identified health needs can enhance individual and organizational capacity to address health disparities in rural and underserved communities.

Dean, D. (2014). Perirectal abscess masquerading as cauda equina syndrome in an otherwise healthy 12-year-old child. *Case Reports in Emergency Medicine*, 2014, 817124.

A 12-year-old boy was brought to an urgent care center for fever, back pain, and abnormal gait. In addition to back pain, the patient was found to be persistently febrile but also had decreased perianal sensation and bowel incontinence. He was therefore referred to the emergency department where his back pain improved without medication but he was still febrile with bowel incontinence and persistently decreased perianal sensation. An MRI was ordered to evaluate possible cauda equina syndrome and revealed a perirectal abscess. The child ultimately underwent an exam under anesthesia with pediatric surgery and had a drain placed. This case highlights a unique presentation of perirectal abscess masquerading as cauda equina syndrome. A discussion of important considerations in emergency room diagnosis and management is presented.

Dean, J. M., Bennet, L., Back, S. A., McClendon, E., Riddle, A., & Gunn, A. J. (2014). What brakes the preterm brain? an arresting story. *Pediatric Research*, 75(1-2), 227-233.

Children surviving premature birth have a high risk of cognitive and learning disabilities and attention deficit. In turn, adverse outcomes are associated with persistent reductions in cerebral growth on magnetic resonance imaging (MRI). It is striking that modern care has been associated with a dramatic reduction in the risk of cystic white matter damage, but modest improvements in terms of neurodevelopmental impairment. This review will explore the hypothesis that the disability is primarily associated with impaired neural connectivity rather than cell death alone. Very preterm infants exhibit reduced thalamocortical connectivity and cortical neuroplasticity compared with term-born controls. In preterm fetal sheep, moderate cerebral ischemia with no neuronal loss, but significant diffuse failure of maturation of cortical pyramidal neurons, was associated with impaired dendritic growth and synapse formation, consistent with altered connectivity. These changes were associated with delayed decline in cortical fractional anisotropy (FA) on MRI. Supporting these preclinical findings, preterm human survivors showed similar enduring impairment of microstructural development of the cerebral cortex defined by FA, consistent with delayed formation of neuronal processes. These findings offer the promise that better understanding of impairment of neural connectivity may allow us to promote normal development and growth of the cortex after preterm birth. © 2014 International Pediatric Research Foundation, Inc.

Debarber, A. E., Luo, J., Giugliani, R., Souza, C. F., Chiang, J. P., Merkens, L. S., et al. (2014). A useful multi-analyte blood test for cerebrotendinous xanthomatosis. *Clinical Biochemistry*,

OBJECTIVES: Cerebrotendinous xanthomatosis (CTX) is a rare genetic disorder of bile acid (BA) synthesis that can cause progressive neurological damage and premature death. Blood (normally serum or plasma) testing for CTX is performed by a small number of specialized laboratories, routinely by gas chromatography-mass spectrometry (GC-MS) measurement of elevated 5 α -cholestanol. We report here on a more sensitive biochemical approach to test for CTX particularly useful for confirmation of CTX in the case of a challenging diagnostic sample with 5 α -cholestanol that, although elevated, was below the cut-off used for diagnosis of CTX (10 μ g/mL or 1.0mg/dL). DESIGN AND METHODS: We have previously described liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) methodology utilizing keto derivatization to enable the sensitive quantification of plasma ketosterol BA precursors that accumulate in CTX. We have expanded this methodology to perform isotope dilution LC-ESI-MS/MS quantification of a panel of plasma ketosterol BA precursors, with internal standards readily generated using isotopically-enriched derivatization reagent. RESULTS: Quantification of plasma ketosterol BA precursors (7 α -hydroxy-4-cholesten-3-one, 7 α ,12 α -dihydroxy-4-cholesten-3-one and 7 α ,12 α -dihydroxy-5 β -cholestan-3-one) in a single LC-ESI/MS/MS test provided better discrimination between a CTX-positive and negative samples analyzed (n=20) than measurement of 5 α -cholestanol alone. CONCLUSIONS: Quantification of plasma ketosterol BA precursors provides a more sensitive biochemical approach to discriminate between CTX negative and positive samples. A multiplexed LC-ESI-MS/MS test quantifying a panel of plasma ketosterols, with simple sample preparation, rapid analysis time and readily available internal standards, can be performed by most clinical laboratories. Wider availability of testing will benefit those affected with CTX.

Deodhar, A. (2014). Axial spondyloarthritis criteria and modified NY criteria: Issues and controversies. *Clinical Rheumatology*,

The Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis (axSpA) developed in 2009 was a major step forward, since the 1984 modified New York (mNY) criteria for classification of ankylosing spondylitis (AS) were too insensitive to

identify patients with early signs of axial inflammation. In the absence of "diagnostic" criteria for either axSpA or AS, both of these "classification" criteria are routinely used in clinical practice to diagnose patients. However, there is a real danger of "misdiagnosis" if classification criteria are applied erroneously by ticking "yes" or "no" boxes in an undiagnosed patient. This concern was raised and discussed at the FDA Arthritis Advisory Committee meeting in June 2013, and the committee warned that if TNF inhibitors are approved to treat axSpA, such misdiagnosis could lead to serious consequences. To gauge the SPARTAN members' familiarity with these criteria and these issues surrounding them, as well as to investigate how they are using these criteria in daily practice, two questionnaires (one each for mNY and ASAS axSpA criteria) were sent to the "full" members of SPARTAN before the annual meeting. The results showed that more than 60 % of the responders used these criteria most of the time in practice to help them diagnose a patient, and nearly three fourth of responders agreed with the FDA Advisory Committee and would like to see some objective signs before prescribing TNF inhibitors to axSpA patients. A majority of responders looked at the sacroiliac joint x-rays themselves to diagnose sacroiliitis, even though they had difficulty in grading the x-rays. In a live vote at the meeting, 88 % of the members suggested that SPARTAN should engage in either modifying the existing criteria or develop new diagnostic criteria for axial spondyloarthritis.

DeVoe, J. E., Gold, R., Cottrell, E., Bauer, V., Brickman, A., Puro, J., et al. (2014). The ADVANCE network: Accelerating data value across a national community health center network. *Journal of the American Medical Informatics Association*,

The ADVANCE (Accelerating Data Value Across a National Community Health Center Network) clinical data research network (CDRN) is led by the OCHIN Community Health Information Network in partnership with Health Choice Network and Fenway Health. The ADVANCE CDRN will 'horizontally' integrate outpatient electronic health record data for over one million federally qualified health center patients, and 'vertically' integrate hospital, health plan, and community data for these patients, often under-represented in research studies. Patient investigators, community investigators, and academic investigators with diverse expertise will work together to meet project goals related to data integration, patient engagement and recruitment, and the development of streamlined regulatory policies. By enhancing the data and research

infrastructure of participating organizations, the ADVANCE CDRN will serve as a 'community laboratory' for including disadvantaged and vulnerable patients in patient-centered outcomes research that is aligned with the priorities of patients, clinics, and communities in our network. © 2014 by the American Medical Informatics Association.

Devoe, J. E., Tillotson, C. J., Angier, H., & Wallace, L. S. (2014). Recent health insurance trends for US families: Children gain while parents lose. *Maternal and Child Health Journal, 18*(4), 1007-1016.

In the past decade, political and economic changes in the United States (US) have affected health insurance coverage for children and their parents. Most likely these policies have differentially affected coverage patterns for children (versus parents) and for low-income (versus high-income) families. We aimed to examine - qualitatively and quantitatively - the impact of changing health insurance coverage on US families. Primary data from interviews with Oregon families (2008-2010) were analyzed using an iterative process. Qualitative findings guided quantitative analyses of secondary data from the nationally-representative Medical Expenditure Panel Survey (MEPS) (1998-2009); we used Joinpoint Regression to assess average annual percent changes (AAPC) in health insurance trends, examining child and parent status and type of coverage stratified by income. Interviewees reported that although children gained coverage, parents lost coverage. MEPS analyses confirmed this trend; the percentage of children uninsured all year decreased from 9.6 % in 1998 to 6.1 % in 2009; AAPC = -3.1 % (95 % confidence interval [CI] from -5.1 to -1.0), while the percentage of parents uninsured all year rose from 13.6 % in 1998 to 17.1 % in 2009, AAPC = 2.7 % (95 % CI 1.8-3.7). Low-income families experienced the most significant changes in coverage. Between 1998 and 2009, as US children gained health insurance, their parents lost coverage. Children's health is adversely affected when parents are uninsured. Investigation beyond children's coverage rates is needed to understand how health insurance policies and changing health insurance coverage trends are impacting children's health. © 2013 Springer Science+Business Media New York.

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., et al. (2014). Report of the NIH task force on research standards for chronic low back pain. *The Journal of Pain*

: *Official Journal of the American Pain Society,*

Despite rapidly increasing intervention, functional disability due to chronic low back pain (cLBP) has increased in recent decades. We often cannot identify mechanisms to explain the major negative impact cLBP has on patients' lives. Such cLBP is often termed non-specific and may be due to multiple biologic and behavioral etiologies. Researchers use varied inclusion criteria, definitions, baseline assessments, and outcome measures, which impede comparisons and consensus. Therefore, NIH Pain Consortium charged a Research Task Force (RTF) to draft standards for research on cLBP. The resulting multidisciplinary panel recommended using 2 questions to define cLBP; classifying cLBP by its impact (defined by pain intensity, pain interference, and physical function); use of a minimum dataset to describe research participants (drawing heavily on the PROMIS methodology); reporting "responder analyses" in addition to mean outcome scores; and suggestions for future research and dissemination. The Pain Consortium has approved the recommendations, which investigators should incorporate into NIH grant proposals. The RTF believes that these recommendations will advance the field, help to resolve controversies, and facilitate future research addressing the genomic, neurologic, and other mechanistic substrates of chronic low back pain. We expect that the RTF recommendations will become a dynamic document and undergo continual improvement. PERSPECTIVE: A task force was convened by the NIH Pain Consortium with the goal of developing research standards for chronic low back pain. The results included recommendations for definitions, a minimum dataset, reporting outcomes, and future research. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes.

Dimitrova, A., Lou, J. S., Andrea, S., Luo, Y., Murchison, C., & Oken, B. (2014). Local effects of acupuncture on the median and ulnar nerves in patients with carpal tunnel syndrome (CTS): Study design and preliminary results. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A42.

Dobek, J., Winters-Stone, K. M., Bennett, J. A., & Nail, L. (2014). Musculoskeletal changes after 1 year of exercise in older breast cancer survivors. *Journal of Cancer Survivorship*, 8(2), 304-311. Introduction: We have previously reported that 1 year of supervised resistance + impact training

stopped bone loss and built muscle strength in older breast cancer survivors. The purpose of this study was to determine whether these benefits persisted 1 year after completion of the intervention. Methods: Sixty-seven women from the original trial completed baseline and post-intervention body composition and muscle strength tests, and 44 women were available 1 year later for follow-up assessments. Bone mineral density (grams per square centimeter) of the hip and spine, muscle mass (kilograms), and fat mass (kilograms) were measured by dual-energy X-ray absorptiometry and maximal upper and lower body strength were measured by one-repetition maximum tests (kilograms). We compared between group changes across baseline (pre-intervention), 1 (post-intervention), and 2 years (1 year follow up) on study outcomes using repeated-measures analysis of covariance, adjusting for age. Results: Significant group by time interactions were found for spine bone mineral density (BMD) ($p < 0.01$) and lower body muscle strength ($p < 0.05$), with a trend for upper body muscle strength ($p = 0.05$). Spine BMD remained stable across intervention and follow-up periods in exercisers compared with continuous losses in controls across 1- and 2-year periods. In contrast, lower body strength increased in exercisers across the intervention, but decreased to near-baseline levels during follow-up compared with no change over either time period in controls. Conclusions: Our data suggest that spine BMD can be preserved in older breast cancer survivors even after formal exercise training stops; however, muscle strength is not similarly maintained and may require continued participation in a supervised exercise program. Implications for Cancer Survivors: Exercise programs aimed at improving musculoskeletal health should be considered in the long-term care plan for breast cancer survivors. © 2013 Springer Science+Business Media New York.

Dodge, H. H., Zhu, J., Lee, C. -, Chang, C. -. H., & Ganguli, M. (2014). Cohort effects in age-associated cognitive trajectories. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, 69(6), 687-694.

Background. The age-specific prevalence and incidence of dementia and cognitive impairment in the United States have either remained stable or even slightly declined during the 1980s-1990s. A suggested but untested reason for this improvement in cognitive function over time is higher educational attainment among more recent cohorts. Methods. We used data from two large prospective population-based epidemiological dementia studies conducted in two adjacent regions

during the period 1987-2012. We examined whether (i) cohort effects could be observed in age-associated trajectories of cognitive functions and (ii) the observed cohort effects could be explained by educational attainment. Trajectories of neuropsychological tests tapping three domains (psychomotor speed, executive function, and language) were compared among cohorts born between 1902 and 1911, 1912 and 1921, 1922 and 1931, and 1932 and 1943. We examined Age \times Cohort interactions in mixed-effects models with/without controlling for education effects. Results. Cohort effects in age-associated trajectories were observed in all three domains, with consistent differences between the earliest born cohort and the most recent cohort. Executive functions showed the strongest and persistent differences between the most recent and other three cohorts. Education did not attenuate any of these associations. Conclusions. Cohort effects were observed in all examined cognitive domains and, surprisingly, remained significant after controlling for educational effects. Factors other than education are likely responsible for the cohort effects in cognitive decline. © 2013 The Author.

Doty, J. F., Coughlin, M. J., Hirose, C., Stevens, F., Schutt, S., Kennedy, M., et al. (2014). First metatarsocuneiform joint mobility: Radiographic, anatomic, and clinical characteristics of the articular surface. *Foot and Ankle International*, 35(5), 504-511.

Background: The first metatarsocuneiform joint is involved in first ray biomechanics and related forefoot pathology. The purpose of this study was to evaluate the first metatarsocuneiform joint radiographic findings in relation to angular position of the radiographic beam, and to assess the joint mobility as it relates to the anatomic orientation of the facets on both radiographic imaging and gross anatomic dissection. Methods: Thirty-nine cadaveric lower extremity limbs were stratified as normal, mild, moderate, or severe hallux valgus deformity. Mobility of the first metatarsocuneiform joint for each specimen was assessed using the Klaue device. The medial inclination angle (obliquity) of the first metatarsocuneiform joint was determined on both 10-degree and 20-degree anteroposterior radiographs. The lateral inclination angle of both the dorsal and plantar facets was determined on lateral radiographs. Each specimen was then dissected to directly inspect the metatarsocuneiform joint. Results: The metatarsocuneiform joint mean height was 28.3 mm and the mean width was 13.1 mm. Twenty-three feet demonstrated a continuous cartilaginous surface, 15 feet demonstrated a bilobed cartilaginous surface, and 1 foot

demonstrated completely separated facets. Dorsal facets were curved in 37 specimens and flat in 2 specimens. Plantar facets were flat in 30 specimens and curved in 9 specimens. The medial inclination angle measured 15.8 degrees on the 10-degree radiograph and 2.6 degrees on the 20-degree radiograph. We were unable to establish any correlations of metatarsocuneiform joint angles or facet contour with mobility measured by the Klaue device. Conclusions: The metatarsocuneiform joint has a height to width ratio of nearly 2:1. Continuous and bilobed facets are both very common anatomic variants. The contour of the dorsal facet was predominantly curved and the contour of the plantar facet was predominantly flat. First metatarsocuneiform joint mobility does not appear to be dependent on the contour of the facets or the degree of medial inclination of the joint. Clinical Relevance: Anatomic and radiographic findings with regard to mobility of the first metatarsocuneiform joint may assist the surgeon in interpreting the joint's relationship to hallux valgus deformity and to aid in clinical decision making. Our findings suggest that radiographic interpretation of medial inclination is unreliable and should not be used to determine the appropriateness of specific operative procedures. © The Author(s) 2014.

Drobyshevsky, A., Jiang, R., Lin, L., Derrick, M., Luo, K., Back, S. A., et al. (2014). Unmyelinated axon loss with postnatal hypertonia after fetal hypoxia. *Annals of Neurology*, 75(4), 533-541.

Objective White matter (WM) injury due to myelination defects is believed to be responsible for the motor deficits seen in cerebral palsy. We tested the hypothesis that the predominant injury is to functional electrical connectivity in unmyelinated WM fibers by conducting a longitudinal study of central WM tracts in newborn rabbit kits with hypertonia in our model of cerebral palsy.

Methods Pregnant rabbits at 70% gestation underwent 40-minute uterine ischemia. Motor deficits in newborn kits, including muscle hypertonia, were assessed by neurobehavioral testing. Major central WM tracts, including internal capsule, corpus callosum, anterior commissure, and fimbria hippocampi, were investigated for structural and functional injury using diffusion tensor magnetic resonance imaging (MRI), electrophysiological recordings of fiber conductivity in perfused brain slices, electron microscopy, and immunohistochemistry of oligodendrocyte lineage. Results Motor deficits were observed on postnatal day 1 (P1) when WM tracts were unmyelinated. Myelination occurred later and was obvious by P18. Hypertonia was associated with microstructural WM injury and unmyelinated axon loss at P1, diagnosed by diffusion tensor MRI and electron microscopy.

Axonal conductivity from electrophysiological recordings in hypertonic P18 kits decreased only in unmyelinated fibers, despite a loss in both myelinated and unmyelinated axons. Interpretation Motor deficits in cerebral palsy were associated with loss of unmyelinated WM tracts. The contribution of injury to myelinated fibers that was observed at P18 is probably a secondary etiological factor in the motor and sensory deficits in the rabbit model of cerebral palsy. *Ann Neurol* 2014; 75:533-541 © 2014 American Neurological Association.

Drummond, M. B., Buist, A. S., Crapo, J. D., Wise, R. A., & Rennard, S. I. (2014). Chronic obstructive pulmonary disease: NHLBI workshop on the primary prevention of chronic lung diseases. *Annals of the American Thoracic Society*, 11(SUPPL. 3), S154-S160.

Chronic obstructive pulmonary disease (COPD) is a complex set of conditions with multiple risk factors, disease mechanisms, and clinical manifestations. These characteristics make primary prevention of COPD challenging. Semantic issues related to prevalent and incident disease (e.g., the use of specific cut points on a continuous range) should not derail development of primary prevention initiatives. Potential targets for COPD prevention occur along the spectrum of disease development. Understanding risk factors early in life, whether specific to COPD or not, allows for study of interventions to optimize lung function at birth and to prolong the lung function plateau, potentially reducing the development of COPD. It is necessary to identify noninvasive ways to screen for early COPD in those at risk before progression to clinically significant disease.

Identification of specific COPD subgroups, such as individuals with chronic bronchitis, those with α 1-antitrypsin deficiency, or early radiographic changes with normal spirometry, may offer specific opportunities for primary prevention. A better understanding of why COPD progresses despite smoking cessation is needed. Future research initiatives should also focus on identifying the underlying mechanisms and relevant interventions for nonsmokers with COPD, a currently poorly studied group. Ultimately, preventing the development of COPD will serve to reduce the tremendous burden of this chronic disease worldwide. Copyright © 2014 by the American Thoracic Society.

D'Souza, G., Gross, N. D., Pai, S. I., Haddad, R., Anderson, K. S., Rajan, S., et al. (2014). Oral human papillomavirus (HPV) infection in HPV-positive patients with oropharyngeal cancer and their

partners. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*,

PURPOSE: To better understand oral human papillomavirus (HPV) infection and cancer risk among long-term sexual partners of patients with HPV-positive oropharyngeal cancer (HPV-OPC).

PATIENTS AND METHODS: An oral rinse sample, risk factor survey, cancer history, and oral examination (partners only) were collected from patients with HPV-OPC and their partners. Oral rinse samples were evaluated for 36 types of HPV DNA using PGMY 09/11 primers and line-blot hybridization and HPV16 copy number using quantitative polymerase chain reaction. Oral HPV prevalence was compared with infection among those age 45 to 65 years using National Health and Nutrition Examination Survey (NHANES) 2009-2010. **RESULTS:** A total of 164 patients with HPV-OPC and 93 of their partners were enrolled. Patients were primarily men (90%), were never-smokers (51%), and had performed oral sex (97%), with a median age of 56 years; they had a high prevalence of oncogenic oral HPV DNA (61%) and oral HPV16 DNA (54%) at enrollment. Female partners had comparable oncogenic oral HPV prevalence compared with members of the general population of the same age (1.2% v 1.3%). Among the six male partners, no oncogenic oral HPV infections were detected. No precancers or cancers were identified during partner oral cancer screening examinations. However, a history of cervical disease was reported by nine partners (10.3%) and two female patients (11.8%), and three patients (2.0%) reported a previous partner who developed invasive cervical cancer. **CONCLUSION:** Oral HPV16 DNA is commonly detected among patients with HPV-OPC at diagnosis, but not among their partners. Partners of patients with HPV-OPC do not seem to have elevated oral HPV infection compared with the general population.

Earp, M. A., Kelemen, L. E., Magliocco, A. M., Swenerton, K. D., Chenevix-Trench, G., Lu, Y., et al. (2014). Genome-wide association study of subtype-specific epithelial ovarian cancer risk alleles using pooled DNA. *Human Genetics*, 133(5), 481-497.

Epithelial ovarian cancer (EOC) is a heterogeneous cancer with both genetic and environmental risk factors. Variants influencing the risk of developing the less-common EOC subtypes have not been fully investigated. We performed a genome-wide association study (GWAS) of EOC according to subtype by pooling genomic DNA from 545 cases and 398 controls of European

descent, and testing for allelic associations. We evaluated for replication 188 variants from the GWAS [56 variants for mucinous, 55 for endometrioid and clear cell, 53 for low-malignant potential (LMP) serous, and 24 for invasive serous EOC], selected using pre-defined criteria. Genotypes from 13,188 cases and 23,164 controls of European descent were used to perform unconditional logistic regression under the log-additive genetic model; odds ratios (OR) and 95 % confidence intervals are reported. Nine variants tagging six loci were associated with subtype-specific EOC risk at $P < 0.05$, and had an OR that agreed in direction of effect with the GWAS results. Several of these variants are in or near genes with a biological rationale for conferring EOC risk, including ZFP36L1 and RAD51B for mucinous EOC (rs17106154, OR = 1.17, $P = 0.029$, $n = 1,483$ cases), GRB10 for endometrioid and clear cell EOC (rs2190503, $P = 0.014$, $n = 2,903$ cases), and C22orf26/BPIL2 for LMP serous EOC (rs9609538, OR = 0.86, $P = 0.0043$, $n = 892$ cases). In analyses that included the 75 GWAS samples, the association between rs9609538 (OR = 0.84, $P = 0.0007$) and LMP serous EOC risk remained statistically significant at $P < 0.0012$ adjusted for multiple testing. Replication in additional samples will be important to verify these results for the less-common EOC subtypes. © 2013 Springer-Verlag Berlin Heidelberg.

Eastwood, E. C., & Phillips, T. J. (2014). Opioid sensitivity in mice selectively bred to consume or not consume methamphetamine. *Addiction Biology*, 19(3), 370-379.

There has been little investigation of genetic factors and associated mechanisms that influence risk for development of methamphetamine (MA) dependence. Selectively bred mouse lines that exhibit high (MAHDR) or low (MALDR) levels of MA intake in a two-bottle choice MA drinking (MADR) procedure provide a genetic tool for this purpose. These lines were used to determine whether opioid sensitivity and MA intake are genetically associated, because opioid-mediated pathways influence some effects of MA. Sensitivity to the analgesic effects of the μ -opioid receptor (MOP-r) agonist fentanyl (0.05, 0.1, 0.2, 0.4 mg/kg) was examined using two acute thermal tests (hot plate and tail flick) and one chronic pain test (magnesium sulfate abdominal constriction). Locomotor stimulant responses to fentanyl (0.05, 0.1, 0.2, 0.4 mg/kg) and morphine (10, 20, 30 mg/kg) were also examined. In addition, MADR was measured in the progenitor strains [(C57BL/6J (B6), DBA/2J (D2)] of the F2 population from which the selected lines were generated. The MADR lines did not differ in sensitivity to the analgesic effects of

fentanyl; however, MALDR mice exhibited greater locomotor activation than MAHDR mice to both fentanyl and morphine. D2 mice consumed more MA than B6 mice. The line differences for MA consumption and morphine activation recapitulated B6 and D2 strain differences for these two traits, but not strain differences previously found for opioid analgesic responses. These results support a negative genetic correlation between MA consumption and sensitivity to the stimulant effects of opioids and suggest the involvement of MOP-r regulated systems in MA intake.

Ellison, D. H. (2014). Bardoxolone methyl in type 2 diabetes and advanced chronic kidney disease. *New England Journal of Medicine*, 370(18), 1768.

Fair, D. A., & Schlaggar, B. L. (2009). *Brain development and CNS plasticity* Springer New York.

Since the first developmental studies using fMRI there has been an almost logarithmic growth of investigations regarding functional brain development. This growing knowledge, in combination with landmark animal studies of developmental neuroplasticity, has provided us with significant insight into the nature of brain development and how brain maturation might map onto behavior. Throughout this chapter we discuss how a number of related developmental phenomena (e.g., myelination, pruning, spontaneous activity, neuroplasticity, etc.) interact to produce a common trajectory for the typically developing brain. We also point out that much of our knowledge concerning typical development comes from studies examining neuroplasticity. In addition, we highlight the growing evidence suggesting that abnormal neuroplasticity may contribute to neuropsychiatric disorders by altering typical developmental trajectories of many brain interactions across broad cortical and subcortical networks. We emphasize how such phenomena may not only be related to neurological and psychiatric disorders of development, but disorders in adulthood as well. © 2009 Springer-Verlag New York.

Fang, C., Decker, H., & Banker, G. (2014). Axonal transport plays a crucial role in mediating the axon-protective effects of NmNAT. *Neurobiology of Disease*, 68, 78-90.

Deficits in axonal transport are thought to contribute to the pathology of many neurodegenerative diseases. Expressing the slow Wallerian degeneration protein (Wlds) or related nicotinamide mononucleotide adenylyltransferases (NmNATs) protects axons against damage from a broad range of insults, but the ability of these proteins to protect against

inhibition of axonal transport has received little attention. We set out to determine whether these proteins can protect the axons of cultured hippocampal neurons from damage due to hydrogen peroxide or oxygen-glucose deprivation (OGD) and, in particular, whether they can reduce the damage that these agents cause to the axonal transport machinery. Exposure to these insults inhibited the axonal transport of both mitochondria and of the vesicles that carry axonal membrane proteins; this inhibition occurred hours before the first signs of axonal degeneration. Expressing a cytoplasmically targeted version of NmNAT1 (cytNmNAT1) protected the axons against both insults. It also reduced the inhibition of transport when cells were exposed to hydrogen peroxide and enhanced the recovery of transport following both insults. The protective effects of cytNmNAT1 depend on mitochondrial transport. When mitochondrial transport was inhibited, cytNmNAT1 was unable to protect axons against either insult. The protective effects of mitochondrially targeted NmNAT also were blocked by inhibiting mitochondrial transport. These results establish that NmNAT robustly protects the axonal transport system following exposure to OGD and reactive oxygen species and may offer similar protection in other disease models. Understanding how NmNAT protects the axonal transport system may lead to new strategies for neuroprotection in neurodegenerative diseases. © 2014 Elsevier Inc.

Feigelson, H. S., Zeng, C., Pawloski, P. A., Onitilo, A. A., Richards, C. S., Johnson, M. A., et al. (2014).

Does KRAS testing in metastatic colorectal cancer impact overall survival? A comparative effectiveness study in a population-based sample. *PLoS One*, 9(5), e94977.

PURPOSE: Epidermal growth factor receptor (EGFR) inhibitors are approved for treating metastatic colorectal cancer (CRC); KRAS mutation testing is recommended prior to treatment. We conducted a non-inferiority analysis to examine whether KRAS testing has impacted survival in CRC patients. **PATIENTS AND METHODS:** We included 1186 metastatic CRC cases from seven health plans. A cutpoint of July, 2008, was used to define two KRAS testing time period groups: "pre-testing" (n = 760 cases) and "post-testing" (n = 426 cases). Overall survival (OS) was estimated, and the difference in median OS between the groups was calculated. The lower bound of the one-sided 95% confidence interval (CI) for the difference in survival was used to test the null hypothesis of post-testing inferiority. Multivariable Cox regression models were constructed to adjust for covariates. **RESULTS:** The median unadjusted OS was 15.4 months (95% CI: 14.0-

17.5) and 12.8 months (95% CI: 10.0-15.2) in the pre- and post-testing groups, respectively. The OS difference was -2.6 months with one-sided 95% lower confidence bound of -5.13 months, which was less than the non-inferiority margin (-5.0 months, unadjusted $p = 0.06$), leading to a failure to reject inferiority of OS in the post-testing period. In contrast, in the adjusted analysis, OS non-inferiority was identified in the post-testing period ($p = 0.001$). Sensitivity analyses using cutpoints before and after July, 2008, also met the criteria for non-inferiority. CONCLUSION: Implementation of KRAS testing did not influence CRC OS. Our data support the use of KRAS testing to guide administration of EGFR inhibitors for treatment of metastatic CRC without diminished OS.

Fett, N., & Teng, J. M. (2014). Xanthoma striatum palmare associated with nonsyndromic paucity of the interlobular bile ducts. *Cutis*, 93(5), E6-E8.

Flocke, S. A., Clark, E., Antognoli, E., Mason, M. J., Lawson, P. J., Smith, S., et al. (2014). Teachable moments for health behavior change and intermediate patient outcomes. *Patient Education and Counseling*,

OBJECTIVE: Teachable moments (TM) are opportunities created through physician-patient interaction and used to encourage patients to change unhealthy behaviors. We examine the effectiveness of TMs to increase patients' recall of advice, motivation to modify behavior, and behavior change. METHODS: A mixed-method observational study of 811 patient visits to 28 primary care clinicians used audio-recordings of visits to identify TMs and other types of advice in health behavior change talk. Patient surveys assessed smoking, exercise, fruit/vegetable consumption, height, weight, and readiness for change prior to the observed visit and 6-weeks post-visit. RESULTS: Compared to other identified categories of advice (i.e. missed opportunities or teachable moment attempts), recall was greatest after TMs occurred (83% vs. 49-74%). TMs had the greatest proportion of patients change in importance and confidence and increase readiness to change; however differences were small. TMs had greater positive behavior change scores than other categories of advice; however, this pattern was statistically non-significant and was not observed for BMI change. CONCLUSION: TMs have a greater positive influence on several intermediate markers of patient behavior change compared to other categories of advice.

PRACTICE IMPLICATIONS: TMs show promise as an approach for clinicians to discuss behavior change with patients efficiently and effectively.

Fonareva, I., & Oken, B. (2014). Effects of stress-reducing aromatherapy on go-nogo task following acute stress: An evoked related potentials study. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A65.

Freeman, K. A., Smith, K., Adams, E., Mizokawa, S., & Neville-Jan, A. (2013). Is continence status associated with quality of life in young children with spina bifida? *Journal of Pediatric Rehabilitation Medicine*, 6(4), 215-223.

PURPOSE: To evaluate the relationship between child-and parent-reported quality of life (QOL) and bowel and bladder continence among young children with spina bifida (SB). METHODS: 104 children ages 5-12 years and one of their parents/guardians completed the Pediatric Quality of Life Inventory-Generic Form (PedsQL; parent and child) and the Quality of Life in Spina Bifida Questionnaire (QOLSBQ, parent only). Data on continence, child age, and condition-specific variables were obtained by chart review. RESULTS: Parent and child QOL scores (on all measures of QOL) were positively correlated; parents rated child QOL lower than children's self report. QOL scores did not differ based on continence status. Total PedsQL scores were associated with age and mobility based on child report and with mobility based on parent report. CONCLUSIONS: QOL may not be affected by continence status among young children with SB, though demographic (i.e., age) and condition-specific (i.e., functional mobility status) variables appear relevant. Additional research is needed to further evaluate condition-specific variables, other protective variables, and possible measurement issues that influence QOL in young children with SB. © 2013 - IOS Press and the authors. All rights reserved.

Fricano, C. J., Despenza, T., Jr, Frazel, P. W., Li, M., O'Malley, A. J., Westbrook, G. L., et al. (2014). Fatty acids increase neuronal hypertrophy of pten knockdown neurons. *Frontiers in Molecular Neuroscience*, 7, 30.

Phosphatase and tensin homolog (Pten) catalyzes the reverse reaction of PI3K by dephosphorylating PIP3 to PIP2. This negatively regulates downstream Akt/mTOR/S6 signaling resulting in decreased cellular growth and proliferation. Co-injection of a lentivirus knocking Pten

down with a control lentivirus allows us to compare the effects of Pten knockdown between individual neurons within the same animal. We find that knockdown of Pten results in neuronal hypertrophy by 21 days post-injection. This neuronal hypertrophy is correlated with increased p-S6 and p-mTOR in individual neurons. We used this system to test whether an environmental factor that has been implicated in cellular hypertrophy could influence the severity of the Pten knockdown-induced hypertrophy. Implantation of mini-osmotic pumps delivering fatty acids results in increased neuronal hypertrophy and p-S6/p-mTOR staining. These hypertrophic effects were reversed in response to rapamycin treatment. However, we did not observe a similar increase in hypertrophy in response to dietary manipulations of fatty acids. Thus, we conclude that by driving growth signaling with fatty acids and knocking down a critical regulator of growth, Pten, we are able to observe an additive morphological phenotype of increased soma size mediated by the mTOR pathway.

Fu, K. M., Bess, S., Shaffrey, C. I., Smith, J. S., Lafage, V., Schwab, F., et al. (2014). Adult spinal deformity patients treated operatively report greater baseline pain and disability than patients treated nonoperatively: However, deformities differ between age groups. *Spine*, Study Design. Multi-center, prospective analysis of consecutive adult spinal deformity (ASD) patients. Objective. Identify age related radiographic parameters associated with poor health related quality of life (HRQOL) and treatment preferences for ASD. Summary of Background Data. ASD patients report discrepant severities of disability. Understanding age associated differences for reported disability and treatment preferences may improve ASD evaluation and treatment. Methods. Baseline demographic, radiographic and HRQOL values were evaluated in a multicenter, prospective cohort of consecutive ASD patients. Inclusion criteria: ASD, age >18 years, and no prior spine surgery. Patients were divided into those treated operatively (OP) or nonoperatively (NON) and stratified into 3 age groups; G1 = 65 years. HRQOL measures included Scoliosis Research Society questionnaire (SRS-22r), Oswestry Disability Index (ODI), Short Form-36 Health Survey (SF-36). Results. 497 patients (OP = 156, NON = 341), mean age 50.4 years, met inclusion criteria. OP was older (53.3 vs. 49.0 years), had larger scoliosis (49.3 degrees vs. 43.3 degrees), larger sagittal vertical axis (SVA; 33.2 vs. 13.7mm), greater pelvic incidence-lumbar lordosis mismatch (6.6 degrees vs. 3.1 degrees), and worse HRQOL scores

than NON, respectively ($p < 0.05$). Age stratification demonstrated worsening of SVA, spinopelvic alignment (SPA), and HRQOL scores with increasing age ($p < 0.05$). Age/treatment stratification demonstrated younger OP had greater scoliosis than NON (G1OP = 49.9 degrees vs. G1NON = 42.2 degrees ; G2OP = 56 degrees vs. G2NON = 47.2 degrees ; $p < 0.05$) but similar SPA as NON. Older OP had similar scoliosis, but larger SVA than NON (G3OP = 100.6 vs. G3NON = 66.4 mm; $p < 0.05$). OP in all age groups reported worse HRQOL than NON ($p < 0.05$). Conclusions. Poor HRQOL uniformly determined operative treatment for ASD. Spinal deformities differed between age groups. Younger OP had larger scoliosis but similar SPA and SVA than NON. Older OP had similar scoliosis but worse SVA than NON. Age associated differences for poor HRQOL must be considered when evaluating ASD patients.

Furukawa, R., Driessnack, M., & Colclough, Y. (2014). A committee approach maintaining cultural originality in translation. *Applied Nursing Research*, 27(2), 144-146.

Various methods have been used to translate existing assessment tools and clinical nursing materials from one language to another. The method of choice depends on the research objectives, availability of translators, budget, and time. We highlight our experience using the committee approach to translation. This less commonly used approach introduces the concept of cultural consensus building early in the translation process, which is particularly appropriate when languages are culturally and linguistically distant. Our experience centers on the translation of the Primary Communication Inventory (PCI), from English to Japanese, to study first-time parents in Japan. © 2014 Elsevier Inc.

Gaier, E. D., Rodriguiz, R. M., Zhou, J., Ralle, M., Wetsel, W. C., Eipper, B. A., et al. (2014). In vivo and in vitro analyses of amygdalar function reveal a role for copper. *Journal of Neurophysiology*, 111(10), 1927-1939.

Mice with a single copy of the peptide amidating monooxygenase (Pam) gene (PAM+/-) are impaired in contextual and cued fear conditioning. These abnormalities coincide with deficient long-term potentiation (LTP) at excitatory thalamic afferent synapses onto pyramidal neurons in the lateral amygdala. Slice recordings from PAM+/- mice identified an increase in GABAergic tone (Gaier ED, Rodriguiz RM, Ma XM, Sivaramakrishnan S, Bousquet-Moore D, Wetsel WC, Eipper BA,

Mains RE. J Neurosci 30: 13656-13669, 2010). Biochemical data indicate a tissue-specific deficit in Cu content in the amygdala; amygdalar expression of Atox-1 and Atp7a, essential for transport of Cu into the secretory pathway, is reduced in PAM+/- mice. When PAM+/- mice were fed a diet supplemented with Cu, the impairments in fear conditioning were reversed, and LTP was normalized in amygdala slice recordings. A role for endogenous Cu in amygdalar LTP was established by the inhibitory effect of a brief incubation of wild-type slices with bathocuproine disulfonate, a highly selective, cell-impermeant Cu chelator. Interestingly, bathapplied CuSO₄ had no effect on excitatory currents but reversibly potentiated the disynaptic inhibitory current. Bath-applied CuSO₄ was sufficient to potentiate wild-type amygdala afferent synapses. The ability of dietary Cu to affect signaling in pathways that govern fear-based behaviors supports an essential physiological role for Cu in amygdalar function at both the synaptic and behavioral levels. This work is relevant to neurological and psychiatric disorders in which disturbed Cu homeostasis could contribute to altered synaptic transmission, including Wilson's, Menkes, Alzheimer's, and prion-related diseases. © 2014 the American Physiological Society.

Garg, N., Truong, B., Ku, J. H., Devere, T. S., Ehst, B. D., Blauvelt, A., et al. (2014). A novel, short, and simple screening questionnaire can suggest presence of psoriatic arthritis in psoriasis patients in a dermatology clinic. *Clinical Rheumatology*,
Delaying diagnosis of psoriatic arthritis (PsA) can lead to poor quality of life and disability. The purpose of this study is to identify simple questions for dermatologists to screen psoriasis patients for psoriatic arthritis. Data regarding psoriasis and arthritis were prospectively collected by a questionnaire from all psoriasis patients. Patients with joint-related symptoms were assessed by a rheumatologist for the presence of PsA. Retrospectively, the sensitivity and specificity, positive and negative predictive values, likelihood ratios, and posttest probabilities of various screening questions were calculated to identify the best combination of parameters. Of 517 patients seen in dermatology clinic, 117 (22.63 %) were found to have PsA. Four screening questions ("Do you have a history of joint pain or swelling?" "Do you have stiffness in the morning?" "Have you had X-rays taken of your joints?" "Do you have PsA?") with psoriatic nail changes demonstrated high sensitivity and specificity for predicting PsA. A cutoff of three out of these five parameters correctly classified patients with and without PsA with 86.9 % sensitivity,

71.3 % specificity, 53 % positive predictive value (PPV), 93.6 % negative predictive value (NPV), and area under the curve (AUC) of 0.87. Likelihood ratios for individual parameters varied between 1.6 and 3.7, and with a combination of certain parameters, the posttest probability of PsA was 76 %. This is a preliminary data on a potential screening questionnaire which can help dermatologists quickly screen for PsA. All patients not having evaluated by a rheumatologist could have led to underdiagnosis of PsA and potential misclassification. Psoriasis patients seen at a specialty clinic may introduce a referral bias.

Gilbert, E. W., Harrison, V. L., & Sheppard, B. C. (2014). The adrenal psoas sign: Surgical outcomes following a simple technique to maximize removal of extracortical adrenal tissue during bilateral laparoscopic adrenalectomy. *Surgical Endoscopy*,

BACKGROUND: Bilateral laparoscopic adrenalectomy (BLA) is an effective therapy for the management of persistent hypercortisolism in patients after failed transphenoidal pituitary tumor resection for Cushing's disease. Extracortical adrenal tissue has been identified as a source of persistent hypercortisolism and, if not resected along with both adrenal glands, may lead to treatment failure. We report a reliable and reproducible technique called the "psoas sign" for BLA in patients with Cushing's disease which reduces the likelihood of retained extra-adrenal cortical rests and may reduce intraoperative complications. METHODS: A 16-year retrospective review of all consecutive patients who underwent transabdominal BLA at a single tertiary care center was performed. All patients underwent BLA utilizing the psoas sign technique and all procedures were performed replicating these predetermined surgical steps: (1) Identification of the inferior pole of the gland. (2) Identification of the inferior aspect of the adreno-caval groove on the right or the adrenal vein/renal vein confluence on the left. (3) Division of the adrenal vein. (4) Dissection and removal of the adrenal gland with clearance of all retroperitoneal fat overlying the psoas muscle. RESULTS: Between October 1996 and December 2012, 92 patients underwent BLA for refractory Cushing's disease. Patients were predominantly female (90 %) with a median age of 40 years (17-71). There were 3 intraoperative complications (3.2 %), 2 conversions (2.2 %), and 1 death (1.09 %). Four patients were identified as having extracortical rests of adrenal tissue within the retroperitoneal fat (4.3 %). Mean operative time was 272 min (+/-79.25, n = 68) and median estimated blood loss was 50 mL (10-800 mL). CONCLUSIONS: The psoas sign technique provides

a clear view of the adrenal fossa and facilitates careful dissection of the anatomic planes around the adrenal gland. This technique is feasible, reproducible and in our experience allows for safe removal of both adrenal glands and all surrounding extracortical adrenal tissue.

Gilhooly, J., Schumacher, D. J., West, D. C., & Jones, M. D. (2014). The promise and challenge of entrustable professional activities. *Pediatrics*, 133(SUPPL. 2), S78-S79.

Gilman, S. C., Chokshi, D. A., Bowen, J. L., Rugen, K. W., & Cox, M. (2014). Connecting the dots: Interprofessional health education and delivery system redesign at the veterans health administration. *Academic Medicine : Journal of the Association of American Medical Colleges*, Health systems around the United States are embracing new models of primary care using interprofessional team-based approaches in pursuit of better patient outcomes, higher levels of satisfaction among patients and providers, and improved overall value. Less often discussed are the implications of new models of care for health professions education, including education for physicians, nurse practitioners, physician assistants, and other professions engaged in primary care. Described here is the interaction between care transformation and redesign of health professions education at the largest integrated delivery system in the United States: the Veterans Health Administration (VA). Challenges and lessons learned are discussed in the context of a demonstration initiative, the VA Centers of Excellence in Primary Care Education. Five sites, involving VA medical centers and their academic affiliates in Boise, Cleveland, San Francisco, Seattle, and West Haven, introduced interprofessional primary care curricula for resident physicians and nurse practitioner students beginning in 2011. Implementation struggles largely revolved around the operational logistics and cultural disruption of integrating educational redesign for medicine and nursing and facilitating the interface between educational and clinical activities. To realize new models for interprofessional teaching, faculty, staff, and trainees must understand the histories, traditions, and program requirements across professions and experiment with new approaches to achieving a common goal. Key recommendations for redesign of health professions education revolve around strengthening the union between interprofessional learning, team-based practice, and high-value care.

Goetsch, M. F., Lim, J. Y., & Caughey, A. B. (2014). Locating pain in breast cancer survivors experiencing dyspareunia: A randomized controlled trial. *Obstetrics and Gynecology*,

OBJECTIVE:: To locate sites of genital tenderness in breast cancer survivors not using estrogen who experience dyspareunia and to test the hypothesis that tenderness is limited to the vulvar vestibule rather than the vagina and is reversed by topical anesthetic. METHODS:: Postmenopausal survivors of breast cancer with moderate and severe dyspareunia were recruited for an examination including randomization to a double-blind intervention using topical aqueous 4% lidocaine or normal saline for 3 minutes to the areas found to be tender. Comparisons of changes in patients' reported numerical rating scale values were made with the Wilcoxon rank-sum test with significance set at $P < .05$. RESULTS:: Forty-nine patients aged 37-69 years (mean 55.6 +/- 8.6 years) had a median coital pain score of 8 (interquartile range 7-9, scale 0-10). On examination, all women had tenderness in the vulvar vestibule (worst site 4 o'clock median 6, 4-7). In addition, one had significant vaginal mucosal tenderness and two had pelvic floor myalgia. All had vulvovaginal atrophy with 86% having no intravaginal discharge. Aqueous lidocaine 4% reduced the vestibular tenderness of all painful sites. For example, pain at the worst site changed from a median of 5 (4-7) to 0 (0-1) as compared with saline placebo, which changed the worst site score from 6 (4-7) to 4 (3-6) ($P < .001$). After lidocaine application, speculum placement was nontender in the 47 without either myalgia or vaginal mucosal tenderness. CONCLUSION:: In breast cancer survivors with dyspareunia, exquisite sensitivity was vestibular and reversible with aqueous lidocaine. Vaginal tenderness was rare despite severe atrophy. CLINICAL TRIAL REGISTRATION:: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01539317. LEVEL OF EVIDENCE:: I.

Goetsch, M. F., Lim, J. Y., & Caughey, A. B. (2014). A solution for dyspareunia in breast cancer survivors: A randomized controlled study. *Obstetrics and Gynecology*, 123 Suppl 1, 1S.

INTRODUCTION: Research has focused on vaginal atrophy as the cause of dyspareunia in postmenopausal women. This study explored whether penetrative pain was prevented after hypoestrogenic patients applied analgesic liquid to the vulvar vestibule. METHODS: In a randomized controlled, double-blind trial, estrogen-deficient breast cancer survivors with severe penetrative dyspareunia applied either saline or 4% aqueous lidocaine to the vulvar vestibule for

3 minutes before vaginal penetration. After a 1-month blinded trial using diary documentation of twice-weekly tampon insertion or intercourse, all patients received lidocaine in an open-label trial for 2 months. The primary outcome was penetration pain (0-10 numeric rating scale). Secondary outcomes were sexual distress (Female Sexual Distress Scale, abnormal greater than 11) and resumption of intercourse. Comparisons were made with the Wilcoxon rank sum and Wilcoxon signed rank test, with significance set at $P < .05$. RESULTS: Forty-six patients, screened to exclude pelvic muscle and organ pain, uniformly had severe vulvovaginal atrophy, dyspareunia (median pain 8/10, interquartile range 7-9), and elevated sexual distress scores (median 30.5, interquartile 23-37). Users of lidocaine had less intercourse pain in the blinded phase (median score 1.0 compared with saline 5.3, $P = .015$). After open-label lidocaine use, 37 of 41 (90%) reported comfortable penetration. Sexual distress had decreased (median 14, interquartile range 3-20, $P < .001$). Of 20 abstainers who completed the study, 17 (85%) had resumed penetrative intimacy. No partners complained of numbness. CONCLUSION: Breast cancer survivors with severe menopausal dyspareunia associated with atrophy can have comfortable intercourse after applying topical liquid lidocaine to the vulvar vestibule before penetration.

Goldstein, N. E., Kalman, J., Kutner, J. S., Fromme, E. K., Hutchinson, M. D., Lipman, H. I., et al.

(2014). A study to improve communication between clinicians and patients with advanced heart failure: Methods and challenges behind the working to improve discussions about Defibrillator management (WISDOM) trial. *Journal of Pain and Symptom Management*,

We report the challenges of the Working to Improve Discussions about Defibrillator Management (WISDOM) Trial, our novel, multicenter trial aimed at improving communication between cardiology clinicians and their patients with advanced heart failure (HF) who have implantable cardioverter defibrillators (ICDs). The study objectives are to: 1) increase ICD deactivation conversations; 2) increase the number of ICDs deactivated; and 3) improve psychological outcomes in bereaved caregivers. The unit of randomization is the hospital, the intervention is aimed at HF clinicians, and the patient and caregiver are the units of analysis. Three hospitals were randomized to usual care and three to intervention. The intervention consists of an interactive educational session, clinician reminders, and individualized feedback. We enroll patients with advanced HF and their caregivers, and then we regularly survey them to evaluate

whether the intervention has improved communication between them and their heart failure providers. We encountered three implementation barriers. First, there were Institutional Review Board (IRB) concerns at two sites because of the palliative nature of the study. Second, we had difficulty in creating entry criteria that accurately identified a HF population at high risk of dying. Third, we had to adapt our entry criteria to the changing landscape of ventricular assist devices and cardiac transplant eligibility. Here we present our novel solutions to the difficulties we encountered. Our work has the ability to enhance conduct of future studies focusing on improving care for patients with advanced illness.

Goodrich, E., Wahbeh, H., Mooney, A., Miller, M., & Oken, B. (2014). Teaching mindfulness meditation to adults with severe speech and physical impairments: An exploratory study. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A64.

Grafe, I., Yang, T., Alexander, S., Homan, E. P., Lietman, C., Jiang, M. M., et al. (2014). Excessive transforming growth factor-beta signaling is a common mechanism in osteogenesis imperfecta. *Nature Medicine*,

Osteogenesis imperfecta (OI) is a heritable disorder, in both a dominant and recessive manner, of connective tissue characterized by brittle bones, fractures and extraskeletal manifestations. How structural mutations of type I collagen (dominant OI) or of its post-translational modification machinery (recessive OI) can cause abnormal quality and quantity of bone is poorly understood. Notably, the clinical overlap between dominant and recessive forms of OI suggests common molecular pathomechanisms. Here, we show that excessive transforming growth factor-beta (TGF-beta) signaling is a mechanism of OI in both recessive (*Crtap*^{-/-}) and dominant (*Col1a2tm1.1Mcbr*) OI mouse models. In the skeleton, we find higher expression of TGF-beta target genes, higher ratio of phosphorylated Smad2 to total Smad2 protein and higher in vivo Smad2 reporter activity. Moreover, the type I collagen of *Crtap*^{-/-} mice shows reduced binding to the small leucine-rich proteoglycan decorin, a known regulator of TGF-beta activity. Anti-TGF-beta treatment using the neutralizing antibody 1D11 corrects the bone phenotype in both forms of OI and improves the lung abnormalities in *Crtap*^{-/-} mice. Hence, altered TGF-beta matrix-cell

signaling is a primary mechanism in the pathogenesis of OI and could be a promising target for the treatment of OI.

Green, B. B., Coronado, G. D., Devoe, J. E., & Allison, J. (2014). Navigating the murky waters of colorectal cancer screening and health reform. *American Journal of Public Health, 104*(6), 982-986.

The Affordable Care Act (ACA) mandates that both Medicaid and insurance plans cover life-saving preventive services recommended by the US Preventive Services Task Force, including colorectal cancer (CRC) screening and choice between colonoscopy, flexible sigmoidoscopy, and fecal occult blood testing (FOBT). People who choose FOBT or sigmoidoscopy as their initial test could face high, unexpected, out-of-pocket costs because the mandate does not cover needed follow-up colonoscopies after positive tests. Some people will have no coverage for any CRC screening because of lack of state participation in the ACA or because they do not qualify (e.g., immigrant workers). Existing disparities in CRC screening and mortality will worsen if policies are not corrected to fully cover both initial and follow-up testing.

Grzybowski, A., & Packer, M. (2014). Anticoagulant and antiplatelet therapy during ocular surgery. *The British Journal of Ophthalmology,*

Guc, E., Fankhauser, M., Lund, A. W., Swartz, M. A., & Kilarski, W. W. (2014). Long-term intravital immunofluorescence imaging of tissue matrix components with epifluorescence and two-photon microscopy. *Journal of Visualized Experiments : JoVE, (86)*. doi(86), 10.3791/51388.

Besides being a physical scaffold to maintain tissue morphology, the extracellular matrix (ECM) is actively involved in regulating cell and tissue function during development and organ homeostasis. It does so by acting via biochemical, biomechanical, and biophysical signaling pathways, such as through the release of bioactive ECM protein fragments, regulating tissue tension, and providing pathways for cell migration. The extracellular matrix of the tumor microenvironment undergoes substantial remodeling, characterized by the degradation, deposition and organization of fibrillar and non-fibrillar matrix proteins. Stromal stiffening of the tumor microenvironment can promote tumor growth and invasion, and cause remodeling of blood and lymphatic vessels. Live imaging of matrix proteins, however, to this point is limited to fibrillar

collagens that can be detected by second harmonic generation using multi-photon microscopy, leaving the majority of matrix components largely invisible. Here we describe procedures for tumor inoculation in the thin dorsal ear skin, immunolabeling of extracellular matrix proteins and intravital imaging of the exposed tissue in live mice using epifluorescence and two-photon microscopy. Our intravital imaging method allows for the direct detection of both fibrillar and non-fibrillar matrix proteins in the context of a growing dermal tumor. We show examples of vessel remodeling caused by local matrix contraction. We also found that fibrillar matrix of the tumor detected with the second harmonic generation is spatially distinct from newly deposited matrix components such as tenascin C. We also showed long-term (12 hours) imaging of T-cell interaction with tumor cells and tumor cells migration along the collagen IV of basement membrane. Taken together, this method uniquely allows for the simultaneous detection of tumor cells, their physical microenvironment and the endogenous tissue immune response over time, which may provide important insights into the mechanisms underlying tumor progression and ultimate success or resistance to therapy.

Gupta, S. R., Steele, E. A., & Solomon, A. R. (2014). Idiopathic lymphoplasmacellular mucositis-dermatitis of the eyelid. *Ophthalmic Plastic and Reconstructive Surgery*,

Idiopathic lymphoplasmacellular mucositis-dermatitis is a rare mucosal or cutaneous disorder characterized clinically by papules or plaques with variable erosion and microscopically by dense dermal inflammatory cell infiltrates with numerous plasma cells. It has been described in the oral and upper aerodigestive tracts, male and female genitalia, and other mucosal surfaces. In this article, the authors describe a case of idiopathic lymphoplasmacellular mucositis-dermatitis occurring in the skin of the eyelid that was removed by excisional biopsy and has not recurred in the 19-month follow-up period.

Gur, I., Diggs, B. S., & Orloff, S. L. (2014). Surgical portosystemic shunts in the era of TIPS and liver transplantation are still relevant. *Hpb*, 16(5), 481-493.

Background The surgical portosystemic shunts (PSS) are a time-proven modality for treating portal hypertension. Recently, in the era of liver transplantation and the transjugular intrahepatic portosystemic shunts (TIPS), use of the PSS has declined. Objectives This study was conducted

to evaluate changes in practice, referral patterns, and short- and longterm outcomes of the use of the surgical PSS before and after the introduction of the Model for End-stage Liver Disease (MELD). Methods A retrospective analysis of 47 patients undergoing PSS between 1996 and 2011 in a single university hospital was conducted. Results Subgroups of patients with cirrhosis (53%), Budd-Chiari syndrome (13%), portal vein thrombosis (PVT) (26%), and other pathologies (9%) differed significantly with respect to shunt type, Child-Pugh class, MELD score and perioperative mortality. Perioperative mortality at 60 days was 15%. Five-year survival was 68% (median: 70 months); 5-year shunt patency was 97%. Survival was best in patients with PVT and worst in those with Budd-Chiari syndrome compared to other subgroups. Patency was better in the subgroups of patients with cirrhosis and other pathologies compared with the PVT subgroup. Substantial changes in referral patterns coincided with the adoption of the MELD in 2002, with decreases in the incidence of cirrhosis and variceal bleeding, and increases in non-cirrhotics and hypercoagulopathy. Conclusions Although the spectrum of diseases benefiting from surgical PSS has changed, surgical shunts continue to constitute an important addition to the surgical armamentarium. Selected subgroups with variceal bleeding in well-compensated cirrhosis and PVT benefit from the excellent longterm patency offered by the surgical PSS. © 2013 International Hepato-Pancreato-Biliary Association.

Haley, K. M., Russell, T. B., Boshkov, L., Leger, R. M., Garratty, G., Recht, M., et al. (2014). Fatal carboplatin-induced immune hemolytic anemia in a child with a brain tumor. *Journal of Blood Medicine*, 5, 55-58.

Drug-induced immune hemolytic anemia (DIIHA) is an uncommon side effect of pharmacologic intervention. A rare mediator of DIIHA, carboplatin is an agent used to treat many pediatric cancers. We describe here, the first case of fatal carboplatin induced DIIHA in a pediatric patient and a brief review of the literature. Our patient developed acute onset of multi-organ failure with evidence of complement activation, secondary to a drug induced red cell antibody. Early recognition of the systemic insult associated with carboplatin induced hemolytic anemia may allow for future affected patients to receive plasmapheresis, a potentially effective therapy.

Hansen, L., Leo, M. C., Chang, M. F., Zucker, B. L., & Sasaki, A. (2014). Pain and self-care behaviours in adult patients with end-stage liver disease: A longitudinal description. *Journal of Palliative Care, 30*(1), 32-40.

This prospective descriptive study investigated pain characteristics in 20 outpatients with end-stage liver disease (ESLD) who were approaching the end of life, described variability in pain between and within patients, and described the pharmacological and nonpharmacological pain management strategies used. The instruments we utilized were the Brief Pain Inventory (BPI) and the self-care behaviour (SCB) log for pain. Data were collected once a month over a six-month period. BPI severity of, and interference from pain mean scores ranged from 5.52 to 6.03 and 5.36 to 6.64, respectively. The top three pain-relieving behaviours reported by patients were "taking pain medication," "taking a nap," and "asking for help." Pain medication intake differed between patients who were pursuing a liver transplant and those who were not eligible for one. If we are to effectively improve care for ESLD patients, it is essential that we understand the ways in which these patients experience pain and the pain management strategies they employ. © 2014 Institut universitaire de g riatrie de Montr al.

Harriff, M. J., Cansler, M. E., Toren, K. G., Canfield, E. T., Kwak, S., Gold, M. C., et al. (2014). Human lung epithelial cells contain mycobacterium tuberculosis in a late endosomal vacuole and are efficiently recognized by CD8+ T cells. *PloS One, 9*(5), e97515.

Mycobacterium tuberculosis (Mtb) is transmitted via inhalation of aerosolized particles. While alveolar macrophages are thought to play a central role in the acquisition and control of this infection, Mtb also has ample opportunity to interact with the airway epithelium. In this regard, we have recently shown that the upper airways are enriched with a population of non-classical, MR1-restricted, Mtb-reactive CD8+ T cells (MAIT cells). Additionally, we have demonstrated that Mtb-infected epithelial cells lining the upper airways are capable of stimulating IFN γ production by MAIT cells. In this study, we demonstrate that airway epithelial cells efficiently stimulate IFN γ release by MAIT cells as well as HLA-B45 and HLA-E restricted T cell clones. Characterization of the intracellular localization of Mtb in epithelial cells indicates that the vacuole occupied by Mtb in epithelial cells is distinct from DC in that it acquires Rab7 molecules and does not retain markers of early endosomes such as Rab5. The Mtb vacuole is also heterogeneous as

there is a varying degree of association with Lamp1 and HLA-I. Although the Mtb vacuole shares markers associated with the late endosome, it does not acidify, and the bacteria are able to replicate within the cell. This work demonstrates that Mtb infected lung epithelial cells are surprisingly efficient at stimulating IFN γ release by CD8 $^+$ T cells.

Harrington, C. A., Stevens, S., Stenzel-Poore, M., & Simon, R. P. (2007). *Gene expression profiling in ischemic brain injury and ischemic tolerance* Springer US.

Potent endogenous mechanisms of neuroprotection are encoded in the genome, and the expression of a subset of these genes helps to determine whether cells survive ischemia. A genomic approach may identify and characterize these genes and the neuroprotective pathways through which their protein products operate. Identification of gene products that are endogenous neuroprotectants contributes significantly to our understanding of the pathophysiology of ischemic neuronal injury and would point the way toward new therapeutic approaches to stroke and related disorders such as traumatic brain injury. Here we review a strategy for discovering neuroprotective genes in ischemia by the use of mouse models of ischemic tolerance and microarray analysis to identify genes that are transcriptionally regulated in tolerance. We provide Affymetrix microarray analysis of an ischemic tolerance data set and review in detail the approach to genomic screening. © 2007 Springer-Verlag US.

Harris, M. A., Wagner, D. V., Heywood, M., Hoehn, D., Bahia, H., & Spiro, K. (2014). Youth repeatedly hospitalized for DKA: Proof of concept for novel interventions in children's healthcare (NICH). *Diabetes Care*, 37(6), e125-6.

Harrison, F. E., Bowman, G. L., & Polidori, M. C. (2014). Ascorbic acid and the brain: Rationale for the use against cognitive decline. *Nutrients*, 6(4), 1752-1781.

This review is focused upon the role of ascorbic acid (AA, vitamin C) in the promotion of healthy brain aging. Particular attention is attributed to the biochemistry and neuronal metabolism interface, transport across tissues, animal models that are useful for this area of research, and the human studies that implicate AA in the continuum between normal cognitive aging and age-related cognitive decline up to Alzheimer's disease. Vascular risk factors and comorbidity

relationships with cognitive decline and AA are discussed to facilitate strategies for advancing AA research in the area of brain health and neurodegeneration.

Hartung, D. M., McCarty, D., Fu, R., Wiest, K., Chalk, M., & Gastfriend, D. R. (2014). Extended-release naltrexone for alcohol and opioid dependence: A meta-analysis of healthcare utilization studies. *Journal of Substance Abuse Treatment*,
Through improved adherence, once-monthly injectable extended-release naltrexone (XR-NTX) may provide an advantage over other oral agents approved for alcohol and opioid dependence treatment. The objective of this study was to evaluate cost and utilization outcomes between XR-NTX and other pharmacotherapies for treatment of alcohol and opioid dependence. Published studies were identified through comprehensive search of two electronic databases. Studies were included if they compared XR-NTX to other approved medicines and reported economic and healthcare utilization outcomes in patients with opioid or alcohol dependence. We identified five observational studies comparing 1,565 patients using XR-NTX to other therapies over 6 months. Alcohol dependent XR-NTX patients had longer medication refill persistence versus acamprosate and oral naltrexone. Healthcare utilization and costs was generally lower or as low for XR-NTX-treated patients relative to other alcohol dependence agents. Opioid dependent XR-NTX patients had lower inpatient substance abuse-related utilization versus other agents and \$8170 lower total cost versus methadone.

Hata, T. R., Audish, D., Kotol, P., Coda, A., Kabigting, F., Miller, J., et al. (2014). A randomized controlled double-blind investigation of the effects of vitamin D dietary supplementation in subjects with atopic dermatitis. *Journal of the European Academy of Dermatology and Venereology*, 28(6), 781-789.

Background Subjects with atopic dermatitis (AD) have defects in antimicrobial peptide (AMP) production possibly contributing to an increased risk of infections. In laboratory models, vitamin D can alter innate immunity by increasing AMP production. Objective To determine if AD severity correlates with baseline vitamin D levels, and to test whether supplementation with oral vitamin D alters AMP production in AD skin. Methods This was a multi-centre, placebo-controlled, double-blind study in 30 subjects with AD, 30 non-atopic subjects, and 16 subjects with psoriasis.

Subjects were randomized to receive either 4000 IU of cholecalciferol or placebo for 21 days. At baseline and day 21, levels of 25-hydroxyvitamin D (25OHD), cathelicidin, HBD-3, IL-13, and Eczema Area and Severity Index (EASI) and Rajka-Langeland scores were obtained. Results At baseline, 20% of AD subjects had serum 25OHD below 20 ng/mL. Low serum 25OHD correlated with increased Fitzpatrick Skin Type and elevated BMI, but not AD severity. After 21 days of oral cholecalciferol, mean serum 25OHD increased, but there was no significant change in skin cathelicidin, HBD-3, IL-13 or EASI scores. Conclusions This study illustrated that darker skin types and elevated BMI are important risk factors for vitamin D deficiency in subjects with AD, and highlighted the possibility that seasonality and locale may be potent contributors to cathelicidin induction through their effect on steady state 25OHD levels. Given the molecular links between vitamin D and immune function, further study of vitamin D supplementation in subjects with AD is warranted. © 2013 European Academy of Dermatology and Venereology.

Helms, C. M., Park, B., & Grant, K. A. (2014). Adrenal steroid hormones and ethanol self-administration in male rhesus macaques. *Psychopharmacology*,
RATIONALE: Hypothalamic-pituitary-adrenal (HPA) axis hormones have neuroactive metabolites with receptor activity similar to ethanol. OBJECTIVES: The present study related HPA hormones in naive monkeys to ethanol self-administration. METHODS: Morning plasma adrenocorticotrophic hormone (ACTH), cortisol, deoxycorticosterone (DOC), aldosterone, and dehydroepiandrosterone-sulfate (DHEA-S) were measured longitudinally in male rhesus macaques (*Macaca mulatta*) induced to drink ethanol followed by access to ethanol (4 % w/v, in water) and water 22 h/day for 12 months. RESULTS: During ethanol access, DOC increased among non-heavy (average intake over 12 months 3.0 g/kg/day, n = 9); aldosterone was greater among heavy drinkers after 6 months. The ratio of DOC/aldosterone decreased only among heavy drinkers after 6 or 12 months of ethanol self-administration. ACTH only correlated significantly with DHEA-S, the ratio of cortisol/DHEA-S and DOC after the onset of ethanol access, the former two just in heavy drinkers. Baseline hormones did not predict subsequent ethanol intake over 12 months, but baseline DOC correlated with average blood-ethanol concentrations (BECs), among all monkeys and heavy drinkers as a group. During ethanol access, aldosterone and DOC correlated and tended to correlate, respectively, with 12-month average ethanol intake. CONCLUSIONS: Ethanol

self-administration lowered ACTH and selectively altered its adrenocortical regulation.

Mineralocorticoids may compensate for adrenocortical adaptation among heavy drinkers and balance fluid homeostasis. As DOC was uniquely predictive of future BEC and not water intake, to the exclusion of aldosterone, GABAergic neuroactive metabolites of DOC may be risk factors for binge drinking to intoxication.

Hildebran, C., Cohen, D. J., Irvine, J. M., Foley, C., O'Kane, N., Beran, T., et al. (2014). How clinicians use prescription drug monitoring programs: A qualitative inquiry. *Pain Medicine (Malden, Mass.)*,

OBJECTIVES: Prescription drug monitoring programs (PDMPs) are now active in most states to assist clinicians in identifying potential controlled drug misuse, diversion, or excessive prescribing. Little is still known about the ways in which they are incorporated into workflow and clinical decision making, what barriers continue to exist, and how clinicians are sharing PDMP results with their patients. DESIGN: Qualitative data were collected through online focus groups and telephone interviews. SETTING: Clinicians from pain management, emergency and family medicine, psychiatry/behavioral health, rehabilitation medicine, internal medicine and dentistry participated. PATIENTS: Thirty-five clinicians from nine states participated. METHODS: We conducted two online focus groups and seven telephone interviews. A multidisciplinary team then used a grounded theory approach coupled with an immersion-crystallization strategy for identifying key themes in the resulting transcripts. RESULTS: Some participants, mainly from pain clinics, reported checking the PDMP with every patient, every time. Others checked only for new patients, for new opioid prescriptions, or for patients for whom they suspected abuse. Participants described varied approaches to sharing PDMP information with patients, including openly discussing potential addiction or safety concerns, avoiding discussion altogether, and approaching discussion confrontationally. Participants described patient anger or denial as a common response and noted the role of patient satisfaction surveys as an influence on prescribing. CONCLUSION: Routines for accessing PDMP data and how clinicians respond to it vary widely. As PDMP use becomes more widespread, it will be important to understand what approaches are most effective for identifying and addressing unsafe medication use.

Hitchcock, L. N., Cunningham, C. L., & Lattal, K. M. (2014). Cue configuration effects in acquisition and extinction of a cocaine-induced place preference. *Behavioral Neuroscience, 128*(2), 217-227.

A pervasive finding in animal models of substance abuse is that associations form quickly between contexts and drugs of abuse, such as cocaine. Studies of conditioned place preference (CPP) demonstrate that animals approach cues previously paired with cocaine. This is a commonly used preparation, but the configuration of the CPP apparatus differs across laboratories. Two common apparatus configurations for CPP are one compartment (in which the animal has access to the entire apparatus and spatial cues are irrelevant) or two compartments (in which access is restricted to one half of the apparatus and spatial cues are relevant). We compared the effects of acquisition and extinction of cocaine-induced CPP as a function of configuration. During CPP acquisition, C57BL/6J mice received cocaine paired with one tactile floor (conditioned stimulus; CS+) and saline paired with the other (CS-). CS+ and CS- trials occurred on alternate days in one of three configurations: one-compartment (exposure to the entire apparatus during CS+ or CS-), two-compartment consistent position (exposure to CS+ or CS- in adjacent, spatially distinct compartments), or two-compartment alternating position (exposure to CS+ or CS- in adjacent compartments that alternated spatial locations across days). A stronger preference for the CS+ floor occurred in two- versus one-compartment groups, with the strongest preference observed when cocaine was paired with alternating chamber positions. In contrast, greater loss of preference occurred after extinction in a one-compartment procedure, regardless of one- or two-compartment acquisition history. These findings suggest that a two-compartment configuration facilitated acquisition but attenuated extinction of a cocaine-induced CPP. The use of different CPP configurations may distinguish the underlying substrates and relevant cues for acquisition and extinction processes in cocaine abuse. (PsycINFO Database Record (c) 2014 APA, all rights reserved).

Holbein, M. E., Berglund, J. P., O'Reilly, E. K., Hartman, K., Speicher, L. A., Adamo, J. E., et al. (2014). Recommendations from the investigational new Drug/Investigational device exemption task force of the clinical and translational science award consortium: Developing and implementing a sponsor-investigators training program. *Journal of Investigative Medicine : The Official Publication of the American Federation for Clinical Research, 62*(5), 797-803.

OBJECTIVE: The objective of this study was to provide recommendations for provision of training for sponsor and investigators at Academic Health Centers. **BACKGROUND:** A subgroup of the Investigational New Drug/Investigational Device Exemption (IND/IDE) Task Force of the Clinical and Translational Science Award (CTSA) program Regulatory Knowledge Key Function Committee was assembled to specifically address how clinical investigators who hold an IND/IDE and thus assume the role of sponsor-investigators are adequately trained to meet the additional regulatory requirements of this role. **METHODS:** The participants who developed the recommendations were representatives of institutions with IND/IDE support programs. Through an informal survey, the task force determined that a variety and mix of models are used to provide support for IND/IDE holders within CTSA institutions. In addition, a CTSA consortium-wide resources survey was used. The participants worked from the models and survey results to develop consensus recommendations to address institutional support, training content, and implementation. **RECOMMENDATIONS:** The CTSA IND/IDE Task Force recommendations are as follows: (1) Institutions should assess the scope of Food and Drug Administration-regulated research, perform a needs analysis, and provide resources to implement a suitable training program; (2) The model of training program should be tailored to each institution; (3) The training should specifically address the unique role of sponsor-investigators, and the effectiveness of training should be evaluated regularly by methods that fit the model adopted by the institution; and (4) Institutional leadership should mandate sponsor-investigator training and effectively communicate the necessity and availability of training.

Home, P., Riddle, M., Cefalu, W. T., Bailey, C. J., Bretzel, R. G., Del Prato, S., et al. (2014). Insulin therapy in people with type 2 diabetes: Opportunities and challenges? *Diabetes Care*, 37(6), 1499-1508.

Given the continued interest in defining the optimal management of individuals with type 2 diabetes, the Editor of *Diabetes Care* convened a working party of diabetes specialists to examine this topic in the context of insulin therapy. This was prompted by recent new evidence on the use of insulin in such people. The group was aware of evidence that the benefits of insulin therapy are still usually offered late, and thus the aim of the discussion was how to define the optimal timing and basis for decisions regarding insulin and to apply these concepts in practice. It was

noted that recent evidence had built upon that of the previous decades, together confirming the benefits and safety of insulin therapy, albeit with concerns about the potential for hypoglycemia and gain in body weight. Insulin offers a unique ability to control hyperglycemia, being used from the time of diagnosis in some circumstances, when metabolic control is disturbed by medical illness, procedures, or therapy, as well as in the longer term in ambulatory care. For those previously starting insulin, various other forms of therapy can be added later, which offer complementary effects appropriate to individual needs. Here we review current evidence and circumstances in which insulin can be used, consider individualized choices of alternatives and combination regimens, and offer some guidance on personalized targets and tactics for glycemic control in type 2 diabetes.

Hook, K. V., Huang, T., & Alumkal, J. J. (2014). Orteronel for the treatment of prostate cancer. *Future Oncology (London, England)*, *10*(5), 803-811.

Orteronel (also known as TAK-700) is a novel hormonal therapy that is currently in testing for the treatment of prostate cancer. Orteronel inhibits the 17,20 lyase activity of the enzyme CYP17A1, which is important for androgen synthesis in the testes, adrenal glands and prostate cancer cells. Preclinical studies demonstrate that orteronel treatment suppresses androgen levels and causes shrinkage of androgen-dependent organs, such as the prostate gland. Early reports of clinical studies demonstrate that orteronel treatment leads to reduced prostate-specific antigen levels, a marker of prostate cancer tumor burden, and more complete suppression of androgen synthesis than conventional androgen deprivation therapies that act in the testes alone. Treatment with single-agent orteronel has been well tolerated with fatigue as the most common adverse event, while febrile neutropenia was the dose-limiting toxicity in a combination study of orteronel with docetaxel. Recently, the ELM-PC5 Phase III clinical trial in patients with advanced-stage prostate cancer who had received prior docetaxel was unblinded as the overall survival primary end point was not achieved. However, additional Phase III orteronel trials are ongoing in men with earlier stages of prostate cancer.

Hoover, M. A., Allen, A., La Rochelle, F., Baig-Lewis, S., Pilliod, R., & Caughey, A. B. (2014). Timing delivery of vasa previa: A decision analysis. *Obstetrics and Gynecology*, *123* Suppl 1, 148S-9S.

INTRODUCTION: The objective of this study was to determine the optimal gestational age for delivery in cases of vasa previa. METHODS: A decision-analytic model was designed to compare gestational age of delivery in vasa previa for gestational ages between 32 and 37 weeks using maternal and fetal quality-adjusted life-years in a theoretical cohort of 1,000 women with vasa previa. At each week of gestational age, we allowed for different delivery strategies: 1) premature labor with emergent delivery or 2) planned delivery by cesarean at a predetermined gestational age. Quality-adjusted life-years were calculated based on the probability of fetal bleed or no fetal bleed, with or without development of cerebral palsy, stillbirth, or uncomplicated fetal delivery. RESULTS: Delivery at 33 weeks of gestation for women with vasa previa optimizes maternal and neonatal outcomes, resulting in 6.98 stillbirths per 1,000 and 12.2 cases of cerebral palsy per 1,000. Delivery at 33 weeks of gestation maximizes total quality-adjusted life-years at 56.4. CONCLUSION: Delivery at 33 weeks of gestation for women with vasa previa optimizes maternal and fetal outcomes. (Figure is included in full-text article.).

Hopkins, K., Mowry, J., & Houghton, D. (2013). Congenital oligomeganephronia: Computed tomography appearance. *Clinics and Practice, 3*(2), e31.

We report a case of congenital oligomeganephronia unexpectedly imaged with computed tomography (CT). Oligomeganephronia is a form of renal hypoplasia that leads to renal failure in childhood or adolescence. If encountered, its CT features should suggest the diagnosis and prompt renal biopsy.

Hsieh, W. H., Escobar, C., Yugay, T., Lo, M. T., Pittman-Polletta, B., Salgado-Delgado, R., et al.

(2014). Simulated shift work in rats perturbs multiscale regulation of locomotor activity. *Journal of the Royal Society, Interface / the Royal Society, 11*(96), 10.1098/rsif.2014.0318.

Motor activity possesses a multiscale regulation that is characterized by fractal activity fluctuations with similar structure across a wide range of timescales spanning minutes to hours. Fractal activity patterns are disturbed in animals after ablating the master circadian pacemaker (suprachiasmatic nucleus, SCN) and in humans with SCN dysfunction as occurs with aging and in dementia, suggesting the crucial role of the circadian system in the multiscale activity regulation. We hypothesized that the normal synchronization between behavioural cycles and the SCN-

generated circadian rhythms is required for multiscale activity regulation. To test the hypothesis, we studied activity fluctuations of rats in a simulated shift work protocol that was designed to force animals to be active during the habitual resting phase of the circadian/daily cycle. We found that these animals had gradually decreased mean activity level and reduced 24-h activity rhythm amplitude, indicating disturbed circadian and behavioural cycles. Moreover, these animals had disrupted fractal activity patterns as characterized by more random activity fluctuations at multiple timescales from 4 to 12 h. Intriguingly, these activity disturbances exacerbated when the shift work schedule lasted longer and persisted even in the normal days (without forced activity) following the shift work. The disrupted circadian and fractal patterns resemble those of SCN-lesioned animals and of human patients with dementia, suggesting a detrimental impact of shift work on multiscale activity regulation.

Huang, W., Li, X., Chen, Y., Li, X., Chang, M. C., Oborski, M. J., et al. (2014). Variations of dynamic contrast-enhanced magnetic resonance imaging in evaluation of breast cancer therapy response: A multicenter data analysis challenge. *Translational Oncology*, 7(1), 153-166.

Pharmacokinetic analysis of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) time-course data allows estimation of quantitative parameters such as K (trans) (rate constant for plasma/interstitium contrast agent transfer), v_e (extravascular extracellular volume fraction), and v_p (plasma volume fraction). A plethora of factors in DCE-MRI data acquisition and analysis can affect accuracy and precision of these parameters and, consequently, the utility of quantitative DCE-MRI for assessing therapy response. In this multicenter data analysis challenge, DCE-MRI data acquired at one center from 10 patients with breast cancer before and after the first cycle of neoadjuvant chemotherapy were shared and processed with 12 software tools based on the Tofts model (TM), extended TM, and Shutter-Speed model. Inputs of tumor region of interest definition, pre-contrast T1, and arterial input function were controlled to focus on the variations in parameter value and response prediction capability caused by differences in models and associated algorithms. Considerable parameter variations were observed with the within-subject coefficient of variation (wCV) values for K (trans) and v_p being as high as 0.59 and 0.82, respectively. Parameter agreement improved when only algorithms based on the same model were compared, e.g., the K (trans) intraclass correlation coefficient increased to as high as 0.84.

Agreement in parameter percentage change was much better than that in absolute parameter value, e.g., the pairwise concordance correlation coefficient improved from 0.047 (for K (trans)) to 0.92 (for K (trans) percentage change) in comparing two TM algorithms. Nearly all algorithms provided good to excellent (univariate logistic regression c-statistic value ranging from 0.8 to 1.0) early prediction of therapy response using the metrics of mean tumor K (trans) and $k_{ep} (=K (trans)/v_e$, intravasation rate constant) after the first therapy cycle and the corresponding percentage changes. The results suggest that the interalgorithm parameter variations are largely systematic, which are not likely to significantly affect the utility of DCE-MRI for assessment of therapy response.

Hundal, H., & Cigarroa, J. E. (2014). Saphenous vein grafts intervention: Can adenosine make it better? *Catheterization and Cardiovascular Interventions : Official Journal of the Society for Cardiac Angiography & Interventions*, *83*(7), 1055-1056.

Hutchens, M. P., Fujiyoshi, T., Koerner, I. P., & Herson, P. S. (2014). Extracranial hypothermia during cardiac arrest and cardiopulmonary resuscitation is neuroprotective in vivo. *Therapeutic Hypothermia and Temperature Management*,
There is increasing evidence that ischemic brain injury is modulated by peripheral signaling. Peripheral organ ischemia can induce brain inflammation and injury. We therefore hypothesized that brain injury sustained after cardiac arrest (CA) is influenced by peripheral organ ischemia and that peripheral organ protection can reduce brain injury after CA and cardiopulmonary resuscitation (CPR). Male C57Bl/6 mice were subjected to CA/CPR. Brain temperature was maintained at 37.5 degrees C +/- 0.0 degrees C in all animals. Body temperature was maintained at 35.1 degrees C +/- 0.1 degrees C (normothermia) or 28.8 degrees C +/- 1.5 degrees C (extracranial hypothermia [ExHy]) during CA. Body temperature after resuscitation was maintained at 35 degrees C in all animals. Behavioral testing was performed at 1, 3, 5, and 7 days after CA/CPR. Either 3 or 7 days after CA/CPR, blood was analyzed for serum urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, and interleukin-1beta; mice were euthanized; and brains were sectioned. CA/CPR caused peripheral organ and brain injury. ExHy animals experienced transient reduction in brain temperature after resuscitation (2.1

degrees C +/- 0.5 degrees C for 4 minutes). Surprisingly, ExHy did not change peripheral organ damage. In contrast, hippocampal injury was reduced at 3 days after CA/CPR in ExHy animals (22.4% +/- 6.2% vs. 45.7% +/- 9.1%, $p=0.04$, $n=15/\text{group}$). This study has two main findings. Hypothermia limited to CA does not reduce peripheral organ injury. This unexpected finding suggests that after brief ischemia, such as during CA/CPR, signaling or events after reperfusion may be more injurious than those during the ischemic period. Second, peripheral organ hypothermia during CA reduces hippocampal injury independent of peripheral organ protection. While it is possible that this protection is due to subtle differences in brain temperature during early reperfusion, we speculate that additional mechanisms may be involved. Our findings add to the growing understanding of brain-body cross-talk by suggesting that peripheral interventions can protect the brain even if peripheral organ injury is not altered.

Irvine, J. M., Hallvik, S. E., Hildebran, C., Marino, M., Beran, T., & Deyo, R. A. (2014). Who uses a prescription drug monitoring program and how? insights from a statewide survey of oregon clinicians. *The Journal of Pain : Official Journal of the American Pain Society*,
Prescription drug monitoring programs (PDMP) are relatively new but potentially useful tools to enhance prudent prescribing of controlled substances. However, little is known about the types of clinicians who make most use of PDMPs, how they are incorporated into workflow, or how clinicians and patients respond to the information. We therefore surveyed a random sample of Oregon providers, with 1065 respondents. Clinicians in emergency medicine, primary care, and pain and addiction specialties were the largest number of registrants but many frequent prescribers of controlled substances were not registered to use the PDMP. Among users, 95% reported accessing the PDMP when they suspected a patient of abuse or diversion, but fewer than half would check it for every new patient or every time they prescribe a controlled drug. Nearly all PDMP users reported that they discuss worrisome PDMP data with patients; 54% reported making mental health or substance abuse referrals, and 36% reported sometimes discharging patients from the practice. Clinicians reported frequent patient denial or anger, and only occasional requests for help with drug dependence. More research is needed to optimize how clinicians use PDMPs across settings, and how clinicians and patients respond to the data.
PERSPECTIVE: This study examined differences between PDMP users and non-users and how

clinicians in various specialties use PDMPs in practice. A better understanding of effective PDMP use will facilitate access to treatment for patients with pain, while curbing the prescription drug epidemic, and may ultimately reduce abuse, misuse, and overdose death.

Jarvik, J. G., Comstock, B. A., Heagerty, P. J., Turner, J. A., Sullivan, S. D., Shi, X., et al. (2014).

Back pain in seniors: The back pain outcomes using longitudinal data (BOLD) cohort baseline data. *BMC Musculoskeletal Disorders*, 15(1)

Background: Back pain represents a substantial burden globally, ranking first in a recent assessment among causes of years lived with disability. Though back pain is widely studied among working age adults, there are gaps with respect to basic descriptive epidemiology among seniors, especially in the United States. Our goal was to describe how pain, function and health-related quality of life vary by demographic and geographic factors among seniors presenting to primary care providers with new episodes of care for back pain. Methods. We examined baseline data from the Back pain Outcomes using Longitudinal Data (BOLD) registry, the largest inception cohort to date of seniors presenting to a primary care provider for back pain. The sample included 5,239 patients ≥ 65 years old with a new primary care visit for back pain at three integrated health systems (Northern California Kaiser-Permanente, Henry Ford Health System [Detroit], and Harvard Vanguard Medical Associates [Boston]). We examined differences in patient characteristics across healthcare sites and associations of patient sociodemographic and clinical characteristics with baseline patient-reported measures of pain, function, and health-related quality of life. Results: Patients differed across sites in demographic and other characteristics. The Detroit site had more African-American patients (50%) compared with the other sites (7-8%). The Boston site had more college graduates (68%) compared with Detroit (20%). Female sex, lower educational status, African-American race, and older age were associated with worse functional disability as measured by the Roland-Morris Disability Questionnaire. Except for age, these factors were also associated with worse pain. Conclusions: Baseline pain and functional impairment varied substantially with a number of factors in the BOLD cohort. Healthcare site was an important factor. After controlling for healthcare site, lower education, female sex, African-American race, and older age were associated with worse physical disability and all of these factors except age were associated with worse pain. Trial registration.

Clinical Trials.gov NCT01776242; Registration date: June 13, 2012. © 2014 Jarvik et al.; licensee BioMed Central Ltd.

Jenkins, D. H., Rappold, J. F., Badloe, J. F., Berséus, O., Blackbourne, C. L., Brohi, K. H., et al.

(2014). Trauma hemostasis and oxygenation research position paper on remote damage control resuscitation: Definitions, current practice, and knowledge gaps. *Shock*, 41(SUPPL. 1), 3-12.

The Trauma Hemostasis and Oxygenation Research Network held its third annual Remote Damage Control Resuscitation Symposium in June 2013 in Bergen, Norway. The Trauma Hemostasis and Oxygenation Research Network is a multidisciplinary group of investigators with a common interest in improving outcomes and safety in patients with severe traumatic injury.

The network's mission is to reduce the risk of morbidity and mortality from traumatic hemorrhagic shock, in the prehospital phase of resuscitation through research, education, and training. The concept of remote damage control resuscitation is in its infancy, and there is a significant amount of work that needs to be done to improve outcomes for patients with life-threatening bleeding secondary to injury. The prehospital phase of resuscitation is critical in these patients. If shock and coagulopathy can be rapidly identified and minimized before hospital admission, this will very likely reduce morbidity and mortality. This position statement begins to standardize the terms used, provides an acceptable range of therapeutic options, and identifies the major knowledge gaps in the field. Copyright © 2014 by the Shock Society.

Jindal, S., Gao, D., Bell, P., Albrektsen, G., Edgerton, S. M., Ambrosone, C. B., et al. (2014).

Postpartum breast involution reveals regression of secretory lobules mediated by tissue-remodeling. *Breast Cancer Research*, 16(2)

Introduction: A postpartum diagnosis of breast cancer is an independent predictor of metastases, however the reason is unknown. In rodents, the window of postpartum mammary gland involution promotes tumor progression, suggesting a role for breast involution in the poor prognosis of human postpartum breast cancers. Rodent mammary gland involution is characterized by the programmed elimination of the secretory lobules laid down in preparation for lactation. This tissue involution process involves massive epithelial cell death, stromal remodeling, and immune cell infiltration with similarities to microenvironments present during

wound healing and tumor progression. Here, we characterize breast tissue from premenopausal women with known reproductive histories to determine the extent, duration and cellular mechanisms of postpartum lobular involution in women. Methods: Adjacent normal breast tissues from premenopausal women (n = 183) aged 20 to 45 years, grouped by reproductive categories of nulliparous, pregnant and lactating, and by time since last delivery were evaluated histologically and by special stain for lobular area, lobular type composition, apoptosis and immune cell infiltration using computer assisted quantitative methods. Results: Human nulliparous glands were composed dominantly of small (approximately 10 acini per lobule) and medium (approximately 35 acini per lobule) sized lobules. With pregnancy and lactation, a >10 fold increase in breast epithelial area was observed compared to nulliparous cases, and lactating glands were dominated by mature lobules (>100 acini per lobule) with secretory morphology. Significant losses in mammary epithelial area and mature lobule phenotypes were observed within 12 months postpartum. By 18 months postpartum, lobular area content and lobule composition were indistinguishable from nulliparous cases, data consistent with postpartum involution facilitating regression of the secretory lobules developed in preparation for lactation. Analyses of apoptosis and immune cell infiltrate confirmed that human postpartum breast involution is characterized by wound healing-like tissue remodeling programs that occur within a narrowed time frame. Conclusions: Human postpartum breast involution is a dominant tissue-remodeling process that returns the total lobular area of the gland to a level essentially indistinguishable from the nulliparous gland. Further research is warranted to determine whether the normal physiologic process of postpartum involution contributes to the poor prognosis of postpartum breast cancer. © 2014 Jindal et al.; licensee BioMed Central Ltd.

Johnson, D. F., Malone, L. L., Zalwango, S., Mukisa Oketcho, J., Chervenak, K. A., Thiel, B., et al.

(2014). Tuberculin skin test reversion following isoniazid preventive therapy reflects diversity of immune response to primary mycobacterium tuberculosis infection. *PLoS One*, 9(5), e96613.

RATIONALE: Healthy household contacts (HHC) of individuals with Tuberculosis (TB) with Tuberculin Skin Test (TST) conversions are considered to harbor latent Mycobacterium tuberculosis (Mtb), and at risk for TB. The immunologic, clinical, and public health implications of TST reversions that occur following Isoniazid preventive therapy (IPT) remain controversial.

OBJECTIVES: To measure frequency of TST reversion following IPT, and variation in interferon-gamma (IFN-gamma) responses to Mtb, in healthy Ugandan TB HHC with primary Mtb infection evidenced by TST conversion. METHODS: Prospective cohort study of healthy, HIV-uninfected, TST-negative TB HHC with TST conversions. Repeat TST was performed 12 months following conversion (3 months following completion of 9 month IPT course) to assess for stable conversion vs. reversion. Whole blood IFN-gamma responses to Mtb antigen 85B (MtbA85B) and whole Mtb bacilli (wMtb) were measured in a subset (n = 27 and n = 42, respectively) at enrollment and TST conversion, prior to initiation of IPT. RESULTS: Of 122 subjects, TST reversion was noted in 25 (20.5%). There were no significant differences in demographic, clinical, or exposure variables between reverters and stable converters. At conversion, reverters had significantly smaller TST compared to stable converters (13.7 mm vs 16.4 mm, respectively; $p = 0.003$). At enrollment, there were no significant differences in IFN-gamma responses to MtbA85B or wMTB between groups. At conversion, stable converters demonstrated significant increases in IFN-gamma responses to Ag85B and wMtb compared to enrollment ($p = 0.001$, $p < 0.001$, respectively), while there were no significant changes among reverters. CONCLUSIONS: TST reversion following IPT is common following primary Mtb infection and associated with unique patterns of Mtb-induced IFN-gamma production. We have demonstrated that immune responses to primary Mtb infection are heterogeneous, and submit that prospective longitudinal studies of cell mediated immune responses to Mtb infection be prioritized to identify immune phenotypes protective against development of TB disease.

Kaul, S. (2014). The "no reflow" phenomenon following acute myocardial infarction: Mechanisms and treatment options. *Journal of Cardiology*,

If 'no reflow' is observed within 45min of reperfusion using balloon angioplasty or stent, it is probably related to microthromboemboli, which may also contribute to the extension of the 'no reflow' zone by converting 'low reflow' areas into necrotic ones even when reperfusion is achieved more than 45min after the onset of coronary occlusion. Since 'no reflow' is noted when 45min of coronary occlusion has elapsed even in the absence of a thrombus, 'no reflow' late after reperfusion is predominantly due to tissue necrosis and unlikely to be resolved unless methods to reduce infarct size are used. Attempts at reducing the intracoronary thrombus burden during a

coronary procedure for acute myocardial infarction (AMI) have been shown to reduce 'no reflow' and improve clinical outcome, as has the use of potent antithrombotic agents. Drugs that can reduce infarct size, when given intracoronary or intravenous in conjunction with a coronary intervention during AMI can also reduce 'no reflow' and improve outcomes in patients with AMI. The prognostic importance of 'no reflow' post-AMI is related to its close correspondence with infarct size. Although several imaging and non-imaging methods have been used to assess 'no reflow' or 'low reflow' myocardial contrast echocardiography remains the ideal method for its assessment both in and outside the cardiac catheterization laboratory.

Keyashian, K. (2013). Monitoring and management of toxicities in long-term thiopurine therapy.

Gastroenterology & Hepatology, 9(10), 672-674.

Kim, R., Cingolani, O., Wittstein, I., McLean, R., Han, L., Cheng, K., et al. (2014). Mechanical

alternans is associated with mortality in acute hospitalized heart failure prospective mechanical alternans study (mas). *Circulation: Arrhythmia and Electrophysiology*, 7(2), 259-266.

Background-Acute hospitalized heart failure (AHHF) is associated with 40% to 50% risk of death or rehospitalization within 6 months after discharge. Timely (before hospital discharge) risk stratification of patients with AHHF is crucial. We hypothesized that mechanical alternans (MA) and T-wave alternans (TWA) are associated with postdischarge outcomes in patients with AHHF. Methods and Results-A prospective cohort study was conducted in the intensive cardiac care unit and enrolled 133 patients (59.6 ± 15.7 years; 65% men) admitted with AHHF. Surface ECG and peripheral arterial blood pressure waveform via arterial line were recorded continuously during the intensive cardiac care unit stay. MA and TWA were measured by enhanced modified moving average method. All-cause death or heart transplant served as a combined primary end point. MA was observed in 28 patients (25%), whereas TWA was detected in 33 patients (33%). If present, MA was tightly coupled with TWA. Mean TWA amplitude was larger in patients with both TWA and MA when compared with patients with lone TWA (median, 37 [interquartile range, 26-61] versus 22 [21-23] μV ; $P=0.045$). After a median of 10-month postdischarge, 42 (38%) patients died and 2 had heart transplants. MA was associated with the primary end point in univariable Cox model (hazard ratio, 1.84; 95% confidence interval, 1.00-3.40; $P=0.05$) and after adjustment for

left ventricular ejection fraction, New York Heart Association HF class, and implanted implantable cardioverter defibrillator/ cardiac resynchronization therapy defibrillator (hazard ratio, 2.12 95% confidence interval, 1.13-3.98; P=0.020). TWA without consideration of simultaneous MA was not significantly associated with primary end point (hazard ratio, 1.42; 95% confidence interval, 0.77-2.64; P=0.260). Conclusions-MA is independently associated with outcomes in AHHF. © 2014 American Heart Association, Inc.

Kiyoshi-Teo, H., Cabana, M. D., Froelicher, E. S., & Blegen, M. A. (2014). Adherence to institution-specific ventilator-associated pneumonia prevention guidelines. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses*, 23(3), 201-215.

Background Various institution-specific guidelines have been developed to prevent ventilator-associated pneumonia. However, the availability of guidelines does not ensure adherence to recommended strategies. Objective To identify factors that influence adherence to guidelines for prevention of ventilator-associated pneumonia, with a focus on oral hygiene, head-of-bed elevation, and spontaneous breathing trials. Methods A cross-sectional descriptive study of critical care nurses at 8 hospitals in Northern California was conducted. A survey was created to gather information on possible facilitators of and barriers to adherence to institution-specific guidelines for preventing ventilator-associated pneumonia. User factors, guideline qualities, and contextual factors were explored and tested for possible relationships. Results A total of 576 critical care nurses participated in the survey. Each hospital had unique guidelines for preventing ventilator-associated pneumonia. In general, nurses had positive attitudes and reported adhering to the guidelines always or most of the time. Factors associated with adherence differed according to the intervention implemented. The score on the user attitude scale was the strongest and most consistent predictor of adherence across interventions (odds ratio, 3.49-4.75). Time availability (odds ratio, 1.54) and the level of prioritization (odds ratio, 1.86) were also significant predictors. Conclusion The most consistent facilitator of adherence to guidelines for prevention of ventilator-associated pneumonia was nurses' positive attitude toward the guidelines.

Kleiner, D. E., Berk, P. D., Hsu, J. Y., Courcoulas, A. P., Flum, D., Khandelwal, S., et al. (2014).

Hepatic pathology among patients without known liver disease undergoing bariatric surgery:

Observations and a perspective from the longitudinal assessment of bariatric surgery (LABS) study. *Seminars in Liver Disease*, 34(1), 98-107.

Liver biopsy is not routine during bariatric surgery. Alanine aminotransferase (ALT) is widely used to screen for liver disease. We assessed the relationship between ALT and pathology in biopsies from Longitudinal Assessment of Bariatric Surgery (LABS) patients with normal preoperative ALTs. Biopsies from the LABS-1 and LABS-2 studies were scored using the NASH CRN and Ishak systems. Diagnosis and histology were examined in relation to alanine aminotransferase (ALT) values. Six-hundred ninety-three suitable biopsies were evaluated. Biopsied patients had a median age of 45 years; 78.6% were female and 35.1% diabetic; median body mass index was 46 kg/m². Six-hundred thirty-five biopsied patients had preoperative ALTs. Median ALT was 25 IU/L (interquartile range [IQR] 19-36 IU/L); 26.6% had an ALT > 35 IU/L and 29.9% exceeded the more restrictive Prati criteria for normal. Using the Prati criteria, 7.9% of participants with normal ALT had steatohepatitis and 5.3% had \geq stage 2 fibrosis. Logistic regression models were used to predict the probabilities of having bridging fibrosis/cirrhosis or a diagnosis of borderline/definite steatohepatitis in the unbiopsied LABS-2 sample. The proportion of biopsied participants with these findings was very similar to the modeled results from the unbiopsied cohorts. We estimated that 86.0% of participants with advanced fibrosis and 88.1% of participants with borderline/definite steatohepatitis were not biopsied and went undiagnosed. As ALT did not reliably exclude significant obesity-related liver disease in bariatric surgery patients, consideration should be given to routine liver biopsy during bariatric surgery and medical follow-up of significant hepatic pathology.

Ko, A. L., Weaver, K. E., Hakimian, S., & Ojemann, J. G. (2013). Identifying functional networks using endogenous connectivity in gamma band electrocorticography. *Brain Connectivity*, 3(5), 491-502. Correlations in spontaneous, infra-slow (<0.1 Hz) fluctuations in gamma band (70-100 Hz) signal recorded using electrocorticography (ECoG) reflect the functional organization of the brain, appearing in auditory and visual sensory cortex, motor cortex, and the default mode network (DMN). We have developed a data-driven method using co-modulation in spontaneous, infra-slow, and gamma band power fluctuations in ECoG to characterize the connectivity between cortical areas. A graph spectral clustering algorithm was used to identify networks that appear

consistently. These networks were compared with clinical mapping results obtained using electrocortical stimulation (ECS). We identify networks corresponding to motor and visual cortex with good specificity. Anatomic and functional evidence indicates that other networks, such as the DMN, are also identified by this algorithm. These results indicate that it may be possible to map functional cortex using only spontaneous ECoG recordings. In addition, they support the hypothesis that infra-slow co-modulations of gamma band power represent the neurophysiological basis underlying resting-state networks. Methods examining infra-slow co-modulations in gamma band power will be useful for studying changes in brain connectivity in differing behavioral contexts. Our observations can be made in the absence of observable behavior, suggesting that the electrical mapping of functional cortex is feasible without the use of ECS or task-mediated evoked responses. © Copyright 2013, Mary Ann Liebert, Inc. 2013.

Koerner, I. P., Murphy, S. J., & Hurn, P. D. (2007). *Gender, sex steroids, and cerebral ischemic pathobiology* Springer US.

Biological sex is an important genetic determinant of outcome from cerebral ischemia and clinical stroke. Emerging data suggest that sex, as well as reproductive steroids, shapes ischemic cell death in brain. Female sex steroids, the estrogens and progesterone, provide robust neuroprotection in a variety of experimental settings and strongly contribute to sex-specific responses to ischemia. The purpose of this chapter is: (1) to review the importance of biological sex to ischemic outcome and mechanisms of brain injury, (2) to evaluate the role of female sex steroids as endogenous or exogenous ischemic neuroprotectants, and (3) to review most likely mechanisms by which female sex steroids act to interrupt ischemic cell death pathways. © 2007 Springer-Verlag US.

Komers, R., Xu, B., Fu, Y., McClelland, A., Kantharidis, P., Mittal, A., et al. (2014). Transcriptome-based analysis of kidney gene expression changes associated with diabetes in OVE26 mice, in the presence and absence of losartan treatment. *PLoS One*, 9(5), e96987.

Diabetes is among the most common causes of end-stage renal disease, although its pathophysiology is incompletely understood. We performed next-generation sequencing-based transcriptome analysis of renal gene expression changes in the OVE26 murine model of diabetes

(age 15 weeks), relative to non-diabetic control, in the presence and absence of short-term (seven-day) treatment with the angiotensin receptor blocker, losartan (n = 3-6 biological replicates per condition). We detected 1438 statistically significant changes in gene expression across conditions. Of the 638 genes dysregulated in diabetes relative to the non-diabetic state, >70% were downregulation events. Unbiased functional annotation of genes up- and down-regulated by diabetes strongly associated (p52-fold), encoded by the cationic amino acid transporter Slc7a12, and the gene product most highly downregulated by diabetes (>99%) - encoded by the "pseudogene" Gm6300 - are adjacent in the murine genome, are members of the SLC7 gene family, and are likely paralogous. Therefore, diabetes activates a near-total genetic switch between these two paralogs. Other individual-level changes in gene expression are potentially relevant to diabetic pathophysiology, and novel pathways are suggested. Genes unaffected by diabetes alone but exhibiting increased renal expression with losartan produced a signature consistent with malignant potential.

Konrad-Martin, D., Reavis, K. M., McMillan, G., Helt, W. J., & Dille, M. (2014). Proposed comprehensive ototoxicity monitoring program for VA healthcare (COMP-VA). *Journal of Rehabilitation Research and Development*, 51(1), 81-100.

Prevention and rehabilitation of hearing loss and tinnitus, the two most commonly awarded service-connected disabilities, are high priority initiatives in the Department of Veterans Affairs (VA). At least 4,000 Veterans, most with significant hearing loss, will receive cisplatin this year, with more than half sustaining permanent hearing shift and nearly 40% developing new tinnitus. With improved survivability following cancer treatment, Veterans treated with cisplatin are approached with the dual goals of effective treatment and preserved quality of life. This article describes COMP-VA, a comprehensive ototoxicity monitoring program developed for VA patients receiving cisplatin. The program includes an individualized pretreatment prediction model that identifies the likelihood of hearing shift given cisplatin dose and patient factors. It supports both manual and automated hearing testing with a newly developed portable audiometer capable of performing the recommended procedures on the chemotherapy unit during treatment. It also includes objective methods for identifying outer hair cell changes and predicting audiogram changes using distortion-product otoacoustic emissions. We describe this program of evidence-

based ototoxicity monitoring protocols using a case example to give the reader an understanding of how this program would be applied, along with a plan for future work to accomplish the final stages of program development.

Koo, E., Neuringer, M., & SanGiovanni, J. P. (2014). Macular xanthophylls, lipoprotein-related genes, and age-related macular degeneration. *The American Journal of Clinical Nutrition*,

Plant-based macular xanthophylls (MXs; lutein and zeaxanthin) and the lutein metabolite meso-zeaxanthin are the major constituents of macular pigment, a compound concentrated in retinal areas that are responsible for fine-feature visual sensation. There is an unmet need to examine the genetics of factors influencing regulatory mechanisms and metabolic fates of these 3 MXs because they are linked to processes implicated in the pathogenesis of age-related macular degeneration (AMD). In this work we provide an overview of evidence supporting a molecular basis for AMD-MX associations as they may relate to DNA sequence variation in AMD- and lipoprotein-related genes. We recognize a number of emerging research opportunities, barriers, knowledge gaps, and tools offering promise for meaningful investigation and inference in the field. Overviews on AMD- and high-density lipoprotein (HDL)-related genes encoding receptors, transporters, and enzymes affecting or affected by MXs are followed with information on localization of products from these genes to retinal cell types manifesting AMD-related pathophysiology. Evidence on the relation of each gene or gene product with retinal MX response to nutrient intake is discussed. This information is followed by a review of results from mechanistic studies testing gene-disease relations. We then present findings on relations of AMD with DNA sequence variants in MX-associated genes. Our conclusion is that AMD-associated DNA variants that influence the actions and metabolic fates of HDL system constituents should be examined further for concomitant influence on MX absorption, retinal tissue responses to MX intake, and the capacity to modify MX-associated factors and processes implicated in AMD pathogenesis.

Kost, R. G., Lee, L. N., Yessis, J. L., Wesley, R., Alfano, S., Alexander, S. R., et al. (2014). Research participant-centered outcomes at NIH-supported clinical research centers. *Clinical and Translational Science*,

Background: Although research participation is essential for clinical investigation, few quantitative outcome measures exist to assess participants' experiences. To address this, we developed and deployed a survey at 15 NIH-supported clinical research centers to assess participant-centered outcomes; we report responses from 4,961 participants. Methods: Survey questions addressed core aspects of the research participants' experience, including their overall rating, motivation, trust, and informed consent. We describe participant characteristics, responses to individual questions, and correlations among responses. Results: Respondents broadly represented the research population in sex, race, and ethnicity. Seventy-three percent awarded top ratings to their overall research experience and 94% reported no pressure to enroll. Top ratings correlated with feeling treated with respect, listened to, and having access to the research team ($R^2 = 0.80-0.96$). White participants trusted researchers more (88%) than did nonwhite participants collectively (80%; $p < 0.0001$). Many participants felt fully prepared by the informed consent process (67%) and wanted to receive research results (72%). Conclusions: Our survey demonstrates that a majority of participants at NIH-supported clinical research centers rate their research experience very positively and that participant-centered outcome measures identify actionable items for improvement of participant's experiences, research protections, and the conduct of clinical investigation. © 2014 Wiley Periodicals, Inc.

Kost, R. G., Mervin-Blake, S., Hallarn, R., Rathmann, C., Kolb, H. R., Dennison Himmelfarb, C., et al. (2014). Accrual and recruitment practices at clinical and translational science award (CTSA) institutions: A call for expectations, expertise, and evaluation. *Academic Medicine : Journal of the Association of American Medical Colleges*,
PURPOSE: To respond to increased public and programmatic demand to address underenrollment of clinical translational research studies, the authors examined participant recruitment practices at Clinical and Translational Science Award (CTSA) sites and make recommendations for performance metrics and accountability. METHOD: The CTSA Recruitment and Retention taskforce in 2010 invited representatives at 46 CTSA sites to complete an online 48-question survey querying CTSA accrual and recruitment outcomes, practices, evaluation methods, policies, and perceived gaps in related knowledge/practice. Descriptive statistical and thematic analyses were conducted. RESULTS: Forty-six respondents representing 44 CTSA sites completed the survey.

Recruitment conducted by study teams was the most common practice reported (78%-91%, by study type); 39% reported their institution offered recruitment services to investigators.

Respondents valued study feasibility assessment as a successful practice (39%); desired additional resources included feasibility assessments (49%) and participant registries (44%).

None reported their institution systematically required justification of feasibility; some indicated relevant information was considered prior to institutional review board (IRB) review (30%) or contract approval (22%). All respondents' IRBs tracked study progress, but only 10% of respondents could report outcome data for timely accrual. Few reported written policies addressing poor accrual or provided data to support recruitment practice effectiveness.

CONCLUSIONS: Many CTSA's lack the necessary framework to support study accrual.

Recommendations to enhance accrual include articulating institutional expectations and policy for routine recruitment planning; providing recruitment expertise to inform feasibility assessment and recruitment planning; and developing interdepartmental coordination and integrated informatics infrastructure to drive the conduct, evaluation, and improvement of recruitment practices.

Krashin, J. W., Edelman, A. B., Nichols, M. D., Allen, A. J., Caughey, A. B., & Rodriguez, M. I. (2014).

Prohibiting consent: What are the costs of denying permanent contraception concurrent with abortion care? *American Journal of Obstetrics and Gynecology*,

OBJECTIVES: Oregon and federal laws prohibit giving informed consent for permanent contraception when presenting for an abortion. The primary objective of this study was to estimate the number of unintended pregnancies associated with this barrier to obtaining concurrent tubal occlusion and abortion, compared with the current policy which limits women to obtaining interval tubal occlusion after abortion. The secondary objectives were to compare the financial costs, quality-adjusted life years (QALYs), and the cost effectiveness of these policies.

STUDY DESIGN: We designed a decision-analytic model examining a theoretical population of women who requested tubal occlusion at time of abortion. Model inputs came from the literature. We examined the primary and secondary outcomes stratified by maternal age (above and below 30 years). A Markov model incorporated the possibility of multiple pregnancies. Sensitivity analyses were performed on all variables and a Monte Carlo simulation was conducted. RESULTS:

For every 1,000 women under age 30 in Oregon who did not receive requested tubal occlusion at the time of abortion, over five years there would be 1,274 additional unintended pregnancies and an additional \$4,152,373 in direct medical costs. Allowing women to receive tubal occlusion at time of abortion was the dominant strategy. It resulted in both lower costs and greater QALYs compared to allowing only interval tubal occlusion after abortion. CONCLUSIONS: Prohibiting tubal occlusion at time of abortion resulted in an increased incidence of unintended pregnancy and increased public costs.

Kuehl, K. S., Elliot, D. L., Goldberg, L., MacKinnon, D. P., Vila, B. J., Smith, J., et al. (2014). The safety and health improvement: Enhancing law enforcement departments study: Feasibility and findings. *Frontiers in Public Health*, 2, 38.

This randomized prospective trial aimed to assess the feasibility and efficacy of a team-based worksite health and safety intervention for law enforcement personnel. Four-hundred and eight subjects were enrolled and half were randomized to meet for weekly, peer-led sessions delivered from a scripted team-based health and safety curriculum. Curriculum addressed: exercise, nutrition, stress, sleep, body weight, injury, and other unhealthy lifestyle behaviors such as smoking and heavy alcohol use. Health and safety questionnaires administered before and after the intervention found significant improvements for increased fruit and vegetable consumption, overall healthy eating, increased sleep quantity and sleep quality, and reduced personal stress.

Kumar, N., Radhakrishnan, A., Wright, C. C., Chou, T. -, Lei, H. -, Bolla, J. R., et al. (2014). Crystal structure of the transcriptional regulator Rv1219c of mycobacterium tuberculosis. *Protein Science*, 23(4), 423-432.

The Rv1217c-Rv1218c multidrug efflux system, which belongs to the ATP-binding cassette superfamily, recognizes and actively extrudes a variety of structurally unrelated toxic chemicals and mediates the intrinsic resistance to these antimicrobials in Mycobacterium tuberculosis. The expression of Rv1217c-Rv1218c is controlled by the TetR-like transcriptional regulator Rv1219c, which is encoded by a gene immediately upstream of rv1218c. To elucidate the structural basis of Rv1219c regulation, we have determined the crystal structure of Rv1219c, which reveals a dimeric two-domain molecule with an entirely helical architecture similar to members of the TetR

family of transcriptional regulators. The N-terminal domains of the Rv1219c dimer are separated by a large center-to-center distance of 64 Å . The C-terminal domain of each protomer possesses a large cavity. Docking of small compounds to Rv1219c suggests that this large cavity forms a multidrug binding pocket, which can accommodate a variety of structurally unrelated antimicrobial agents. The internal wall of the multidrug binding site is surrounded by seven aromatic residues, indicating that drug binding may be governed by aromatic stacking interactions. In addition, fluorescence polarization reveals that Rv1219c binds drugs in the micromolar range. © 2014 The Protein Society.

Kumari, N., Corless, C. L., Warrick, A., Beadling, C., Nelson, D., Neff, T., et al. (2014). Mutation profiling in gallbladder cancer in indian population. *Indian Journal of Pathology and Microbiology*, 57(1), 9-12.

Aim: Gallbladder cancer is an aggressive malignancy usually diagnosed at late stage. The molecular genetics of this cancer is heterogeneous and not well established. Mutation profiling of gallbladder cancer was performed through massarray technology with an aim to identify molecular markers involved in the tumor pathogenesis that can be helpful as markers for early diagnosis and targets for therapy. Materials and Methods: Forty nine cases of gallbladder cancer were screened through Sequenom Massarray technology for 390 mutations across 30 genes in formalin fixed paraffin embedded archived tissues and the results of mutation profiling was correlated with tumor characteristics. Mutations were observed in 9 of 49 cases across four genes-TP53 (four cases), CTNNB1 (two cases), PIK3CA (two cases), and KRAS (one case). Six of these cases were well differentiated but of eight of them belonged to stage II to IV disease. Six cases had associated gallstones. Conclusion: The mutation frequency found in gallbladder cancer is comparable to the data available in literature. Identification of PIK3CA and KRAS mutations would help in formulating more efficacious targeted approach for management. Studies with large number of cases would help in exploring more targets and better classification of these cancers at genetic level.

Kwon, E. D., Drake, C. G., Scher, H. I., Fizazi, K., Bossi, A., van den Eertwegh, A. J., et al. (2014). Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant

prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): A multicentre, randomised, double-blind, phase 3 trial. *The Lancet Oncology*, 15(7), 700-712.

BACKGROUND: Ipilimumab is a fully human monoclonal antibody that binds cytotoxic T-lymphocyte antigen 4 to enhance antitumour immunity. Our aim was to assess the use of ipilimumab after radiotherapy in patients with metastatic castration-resistant prostate cancer that progressed after docetaxel chemotherapy. **METHODS:** We did a multicentre, randomised, double-blind, phase 3 trial in which men with at least one bone metastasis from castration-resistant prostate cancer that had progressed after docetaxel treatment were randomly assigned in a 1:1 ratio to receive bone-directed radiotherapy (8 Gy in one fraction) followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for up to four doses. Non-progressing patients could continue to receive ipilimumab at 10 mg/kg or placebo as maintenance therapy every 3 months until disease progression, unacceptable toxic effect, or death. Patients were randomly assigned to either treatment group via a minimisation algorithm, and stratified by Eastern Cooperative Oncology Group performance status, alkaline phosphatase concentration, haemoglobin concentration, and investigator site. Patients and investigators were masked to treatment allocation. The primary endpoint was overall survival, assessed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT00861614. **FINDINGS:** From May 26, 2009, to Feb 15, 2012, 799 patients were randomly assigned (399 to ipilimumab and 400 to placebo), all of whom were included in the intention-to-treat analysis. Median overall survival was 11.2 months (95% CI 9.5-12.7) with ipilimumab and 10.0 months (8.3-11.0) with placebo (hazard ratio [HR] 0.85, 0.72-1.00; $p=0.053$). However, the assessment of the proportional hazards assumption showed that it was violated ($p=0.0031$). A piecewise hazard model showed that the HR changed over time: the HR for 0-5 months was 1.46 (95% CI 1.10-1.95), for 5-12 months was 0.65 (0.50-0.85), and beyond 12 months was 0.60 (0.43-0.86). The most common grade 3-4 adverse events were immune-related, occurring in 101 (26%) patients in the ipilimumab group and 11 (3%) of patients in the placebo group. The most frequent grade 3-4 adverse events included diarrhoea (64 [16%] of 393 patients in the ipilimumab group vs seven [2%] of 396 in the placebo group), fatigue (40 [11%] vs 35 [9%]), anaemia (40 [10%] vs 43 [11%]), and colitis (18 [5%] vs 0). Four (1%) deaths occurred because of toxic effects of the study drug, all in the ipilimumab group. **INTERPRETATION:** Although there was no significant

difference between the ipilimumab group and the placebo group in terms of overall survival in the primary analysis, there were signs of activity with the drug that warrant further investigation.

FUNDING: Bristol-Myers Squibb.

Lebwohl, B., Blaser, M. J., Ludvigsson, J. F., Green, P. H., Rundle, A., Sonnenberg, A., et al. (2014).

The authors reply. *American Journal of Epidemiology*, 179(10), 1275-1276.

Leclair, C. M., Goetsch, M. F., Li, H., & Morgan, T. K. (2014). Histopathologic characteristics of menopausal vestibulodynia. *Obstetrical and Gynecological Survey*, 69(5), 256-257.

Lee, D. J., Djaladat, H., Tadros, N. N., Movassaghi, M., Tejura, T., Duddalwar, V., et al. (2014).

Growing teratoma syndrome: Clinical and radiographic characteristics. *International Journal of Urology*,

Objectives: To present an overview of our surgical experience in the management of growing teratoma syndrome. Methods: A retrospective analysis of all patients undergoing post-chemotherapy retroperitoneal lymphadenectomy between November 2005 and February 2012 revealed 15 patients who met the criteria for growing teratoma syndrome. Their clinical data, imaging characteristics, and surgical and oncological outcomes were reviewed. Results: The median age at diagnosis was 23 years. Primary testis tumors included non-seminomatous germ cell tumor in 12 of 15 patients, seminoma in two of 15 patients and hemorrhagic mass in one patient. Mature teratoma was present in just six (40%) of the orchiectomy specimens. All patients received preoperative chemotherapy. On imaging, the median size of the largest retroperitoneal mass was 7cm (range 3.9-24.5cm). The median rate of linear growth was 0.5cm/month (range 0.03-2.9), and the increase in volume was 9.2cm³/month. All tumors were found to have cystic and necrotic components. Median operative time was 6.2h (range 4.2-15.2h). Estimated blood loss was 600mL (range 100-7000mL), and median length of stay was 5 days (range 3-19 days). Four patients required resection of non-retroperitoneal growing teratoma masses after post-chemotherapy retroperitoneal lymphadenectomy to achieve tumor-free status. There were two minor (Clavien I-II) and two major postoperative complications (Clavien \geq III). All patients are alive and disease free with a median duration of follow-up of 8 months (range 1-64 months). Conclusions: Growing teratoma syndrome tumors vary in their growth rate, but they all

appear to have cystic features with necrosis elements on radiographic evaluation. Aggressive surgical excision is associated with excellent outcomes. © 2014 The Japanese Urological Association.

Lee, V. R., Niu, B., Kaimal, A., Little, S., Nicholson, J., & Caughey, A. B. (2014). Optimal timing of delivery in obese women: A decision analysis. *Obstetrics and Gynecology*, *123 Suppl 1*, 152S-3S.

INTRODUCTION: Maternal obesity complicates over 20% of pregnancies in the United States and increases the risk of many adverse perinatal outcomes. However, limited data exist on the timing of delivery in such cases. The purpose of this study was to determine the optimal gestational age of delivery in an obese patient. METHODS: A decision-analytic model was created using TreeAge software to determine the optimal timing of delivery in a theoretical cohort of 100,000 singleton pregnancies in obese women. Model options ranged from delivery at 37 weeks to 41 weeks of gestation. Strategies involving expectant management until a later gestational age accounted for the probabilities of spontaneous delivery and intrauterine fetal demise at each successive week. Neonatal complications included permanent brachial plexus injury, cerebral palsy, and neonate death. All probability estimates were derived from the literature, and total quality-adjusted life-years were calculated. RESULTS: The lowest rates of neonate death and cerebral palsy were associated with delivery at 39 weeks of gestation, whereas rates of intrauterine fetal demise and brachial plexus injuries were lowest at earlier gestational ages (). Balancing these outcomes, the optimal strategy was delivery at 38 weeks of gestation, which maximized quality-adjusted life-years. Delivery at 38 weeks of gestation would prevent 203 intrauterine fetal demises compared with expectant management until 41 weeks of gestation. Sensitivity analysis found that 38 weeks of gestation remained the optimal strategy until the risks of neonate death and intrauterine fetal demise were 5.57-fold and 1.25-fold, respectively, our baseline assumptions. (Table is included in full-text article.) CONCLUSIONS: : Weighing the risks of intrauterine fetal demise against the risks of neonate death and significant neonatal morbidities, the ideal gestational age to deliver obese women is 38 weeks.

Leshem, Y. A., Gdalevich, M., Ziv, M., David, M., Hodak, E., & Mimouni, D. (2014). Opportunistic infections in patients with pemphigus. *Journal of the American Academy of Dermatology*,

BACKGROUND: Opportunistic infections (OIs) can be defined as infections in immunosuppressed patients that are more frequent or severe because of immunosuppression. The literature on OIs in pemphigus is sparse. **OBJECTIVE:** We assessed the incidence, risk factors, and characteristics of OIs in patients with pemphigus. **METHODS:** This was a historical prospective study following a cohort of 172 patients with newly diagnosed pemphigus for the development of OIs. **RESULTS:** Fourteen patients developed OIs at a mean of 4 months from the time of diagnosis while taking a mean dose of 0.8 mg/kg/day of prednisone, 5 in conjunction with azathioprine. The risk of developing an OI in the first year after the diagnosis of pemphigus was 9.3%, subsequently dropping to 0. Advanced age and possibly diabetes were found to be risk factors for OI development. Infectious agents included *Nocardia*, cytomegalovirus, *Legionella*, and *Listeria*. Two patients died within 2 months of OI diagnosis, and 2 more had neurologic impairment. **LIMITATIONS:** Limitations include the extraction of historical data and the cohort originating from a single geographic region. **CONCLUSION:** OIs present in a significant number of patients with pemphigus during the first year after the diagnosis of pemphigus, with potential deleterious effects. Older and possibly diabetic patients are at increased risk. Physician vigilance and patient education on limiting pathogen exposure is recommended.

Levy, R., Ganjoo, K. N., Leonard, J. P., Vose, J. M., Flinn, I. W., Ambinder, R. F., et al. (2014). Active idiotypic vaccination versus control immunotherapy for follicular lymphoma. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*,

PURPOSE: Idiotypes (Ids), the unique portions of tumor immunoglobulins, can serve as targets for passive and active immunotherapies for lymphoma. We performed a multicenter, randomized trial comparing a specific vaccine (MyVax), comprising Id chemically coupled to keyhole limpet hemocyanin (KLH) plus granulocyte macrophage colony-stimulating factor (GM-CSF) to a control immunotherapy with KLH plus GM-CSF. **PATIENTS AND METHODS:** Patients with previously untreated advanced-stage follicular lymphoma (FL) received eight cycles of chemotherapy with cyclophosphamide, vincristine, and prednisone. Those achieving sustained partial or complete remission (n = 287 [44%]) were randomly assigned at a ratio of 2:1 to receive one injection per month for 7 months of MyVax or control immunotherapy. Anti-Id antibody responses (humoral immune responses [IRs]) were measured before each immunization. The primary end point was

progression-free survival (PFS). Secondary end points included IR and time to subsequent antilymphoma therapy. RESULTS: At a median follow-up of 58 months, no significant difference was observed in either PFS or time to next therapy between the two arms. In the MyVax group (n = 195), anti-Id IRs were observed in 41% of patients, with a median PFS of 40 months, significantly exceeding the median PFS observed in patients without such Id-induced IRs and in those receiving control immunotherapy. CONCLUSION: This trial failed to demonstrate clinical benefit of specific immunotherapy. The subset of vaccinated patients mounting specific anti-Id responses had superior outcomes. Whether this reflects a therapeutic benefit or is a marker for more favorable underlying prognosis requires further study.

Li, M. H., Liu, S. Q., Inoue, K., Lan, J., Simon, R. P., & Xiong, Z. G. (2014). Acid-sensing ion channels in mouse olfactory bulb M/T neurons. *The Journal of General Physiology*, 143(6), 719-731.

The olfactory bulb contains the first synaptic relay in the olfactory pathway, the sensory system in which odorants are detected enabling these chemical stimuli to be transformed into electrical signals and, ultimately, the perception of odor. Acid-sensing ion channels (ASICs), a family of proton-gated cation channels, are widely expressed in neurons of the central nervous system. However, no direct electrophysiological and pharmacological characterizations of ASICs in olfactory bulb neurons have been described. Using a combination of whole-cell patch-clamp recordings and biochemical and molecular biological analyses, we demonstrated that functional ASICs exist in mouse olfactory bulb mitral/tufted (M/T) neurons and mainly consist of homomeric ASIC1a and heteromeric ASIC1a/2a channels. ASIC activation depolarized cultured M/T neurons and increased their intracellular calcium concentration. Thus, ASIC activation may play an important role in normal olfactory function.

Lieberman, D., Holub, J. L., Morris, C. D., Logan, J., Williams, J. L., & Carney, P. (2014). Low rate of large polyps (>9mm) within 10 years after an adequate baseline colonoscopy with no polyps. *Gastroenterology*,

BACKGROUND & AIMS: Guidelines recommend a 10 year interval between screening colonoscopies with negative results for average-risk individuals. However, many patients are examined at shorter intervals. We investigated outcomes of individuals with no polyps who had

repeat colonoscopy in less than 10 years. METHODS: Data were collected using the National Endoscopic Database, from 69 gastroenterology centers, on 264,184 asymptomatic subjects who underwent screening colonoscopies from 2000 through 2006, were found to have no polyps, and received another colonoscopy examination within less than 10 years. RESULTS: No polyps were found in 147,375 patients during a baseline colonoscopy; 17,525 patients (11.9%) had a follow-up colonoscopy within less than 10 years, including 1806 (10.3%) who received the follow-up colonoscopy within less than 1 year. The most common reason for repeating the examination within 1 year was that the first was compromised by inadequate bowel preparation or incomplete examination. Of these patients, 6.5% (95% confidence interval [CI], 5.3-7.6) had large polyp(s) >9 mm—a proportion similar to the prevalence in the average-risk screening population. Reasons that examinations were repeated within 1-5 years included average-risk screening (15.7%), family history of colon polyps or cancer (30.1%), bleeding (31.2%), gastrointestinal symptoms (11.8%), or a positive result from a fecal blood test (5.5%). If the baseline exam was adequate, the incidence of large polyps within 1-5 years after baseline colonoscopy was 3.1% (95% CI, 2.7-3.5) and within years 5-10 years was 3.7% (95% CI, 3.3-4.1). CONCLUSIONS: Repeat colonoscopies within 10 years are of no benefit to patients who had adequate examinations and were found to have no polyps. Repeat colonoscopies are beneficial to patients when the baseline examination was compromised.

Lieberman, D. A., Williams, J. L., Holub, J. L., Morris, C. D., Logan, J. R., Eisen, G. M., et al. (2014). Race, ethnicity, and sex affect risk for polyps greater than 9 mm in average-risk individuals. *Gastroenterology*,

BACKGROUND & AIMS: Colorectal cancer risk differs based on patient demographics. We aimed to measure the prevalence of significant colorectal polyps in average-risk individuals and to determine differences based on age, sex, race, or ethnicity. METHODS: In a prospective study, colonoscopy data were collected, using an endoscopic report generator, from 327,785 average-risk adults who underwent colorectal cancer screening at 84 gastrointestinal practice sites from 2000 to 2011. Demographic characteristics included age, sex, race, and ethnicity. The primary outcome was the presence of suspected malignancy or large polyp(s) >9 mm. The benchmark risk for age to initiate screening was based on white men, 50-54 years old. RESULTS: Risk of

large polyps and tumors increased progressively in men and women with age. Women had lower risks than men in every age group, regardless of race. Blacks had higher risk than whites from ages 50 through 65 years and Hispanics had lower risk than whites from ages 50 through 80 years. The prevalence of large polyps was 6.2% in white men 50-54 years old. The risk was similar among the groups of white women 65-69 years old, Black women 55-59 years old, Black men 50-54 years old, Hispanic women 70-74 years old, and Hispanic men 55-59 years old. The risk of proximal large polyps increased with age, female sex, and Black race. CONCLUSIONS: There are differences in the prevalence and location of large polyp and tumors in average-risk individuals based on age, sex, race, and ethnicity. These findings could be used to select ages at which specific groups should begin colorectal cancer screening.

Lin, Y. C., Li, L., Makarova, A. V., Burgers, P. M., Stone, M. P., & Lloyd, R. S. (2014). Error-prone replication bypass of the primary aflatoxin B1 DNA adduct, AFB1-N7-gua. *The Journal of Biological Chemistry*,

Hepatocellular carcinomas (HCC) are the third leading cause of cancer deaths worldwide. The highest rates of early onset HCC occur in geographical regions with high aflatoxin B1 (AFB1) exposure, concomitant with hepatitis B infection. Although the carcinogenic basis of AFB1 has been ascribed to its mutagenic effects, the mutagenic property of the primary AFB1-DNA adduct, AFB1-N7-Gua, in mammalian cells has not been studied extensively. Taking advantage of the ability to create vectors containing a site-specific DNA adduct, the mutagenic potential was determined in primate cells. This adduct was highly mutagenic following replication in COS-7 cells, with a mutation frequency of 45%. The spectrum of mutations was predominantly G to T base substitutions, a result that is consistent with previous mutation data derived from aflatoxin-associated HCCs. To assess which DNA polymerases might contribute to the mutational outcome, in vitro replication studies were performed. Unexpectedly, replicative polymerase delta and the error-prone translesion synthesis polymerase zeta were able to accurately bypass AFB1-N7-Gua. In contrast, replication bypass using pol kappa was shown to occur with low fidelity and could account for the commonly detected G to T transversions.

Lindestam Arlehamn, C. S., Lewinsohn, D., Sette, A., & Lewinsohn, D. (2014). Antigen for CD4 and CD8 T cells in tuberculosis. *Cold Spring Harbor Perspectives in Medicine*, Tuberculosis (TB), caused by infection with *Mycobacterium tuberculosis* (MTB), represents an important cause of morbidity and mortality worldwide for which an improved vaccine and immunodiagnostics are urgently needed. CD4+ and CD8+ T cells play an important role in host defense to TB. Definition of the antigens recognized by these T cells is critical for improved understanding of the immunobiology of TB and for development of vaccines and diagnostics. Herein, the antigens and epitopes recognized by classically HLA class I- and II-restricted CD4+ and CD8+ T cells in humans infected with MTB are reviewed. Immunodominant antigens and epitopes have been defined using approaches targeting particular TB proteins or classes of proteins and by genome-wide discovery approaches. Antigens and epitopes recognized by classically restricted CD4+ and CD8+ T cells show extensive breadth and diversity in MTB-infected humans.

Lipman, S., Cohen, S., Einav, S., Jeejeebhoy, F., Mhyre, J. M., Morrison, L. J., et al. (2014). The society for obstetric anesthesia and perinatology consensus statement on the management of cardiac arrest in pregnancy. *Anesthesia and Analgesia*, 118(5), 1003-1016. This consensus statement was commissioned in 2012 by the Board of Directors of the Society for Obstetric Anesthesia and Perinatology to improve maternal resuscitation by providing health care providers critical information (including point-of-care checklists) and operational strategies relevant to maternal cardiac arrest. The recommendations in this statement were designed to address the challenges of an actual event by emphasizing health care provider education, behavioral/communication strategies, latent systems errors, and periodic testing of performance. This statement also expands on, interprets, and discusses controversial aspects of material covered in the American Heart Association 2010 guidelines.

Liu, B. S., Tarima, S., Visotcky, A., Pechauer, A., Cooper, R. F., Landsem, L., et al. (2014). The reliability of parafoveal cone density measurements. *The British Journal of Ophthalmology*, BACKGROUND: Adaptive optics scanning light ophthalmoscopy (AOSLO) enables direct visualisation of the cone mosaic, with metrics such as cone density and cell spacing used to

assess the integrity or health of the mosaic. Here we examined the interobserver and inter-instrument reliability of cone density measurements. METHODS: For the interobserver reliability study, 30 subjects with no vision-limiting pathology were imaged. Three image sequences were acquired at a single parafoveal location and aligned to ensure that the three images were from the same retinal location. Ten observers used a semiautomated algorithm to identify the cones in each image, and this was repeated three times for each image. To assess inter-instrument reliability, 20 subjects were imaged at eight parafoveal locations on one AOSLO, followed by the same set of locations on the second AOSLO. A single observer manually aligned the pairs of images and used the semiautomated algorithm to identify the cones in each image. RESULTS: Based on a factorial study design model and a variance components model, the interobserver study's largest contribution to variability was the subject (95.72%) while the observer's contribution was only 1.03%. For the inter-instrument study, an average cone density intraclass correlation coefficient (ICC) of between 0.931 and 0.975 was calculated. CONCLUSIONS: With the AOSLOs used here, reliable cone density measurements can be obtained between observers and between instruments. Additional work is needed to determine how these results vary with differences in image quality.

Lo, D., Zhang, Y., Dai, M. S., Sun, X. X., Zeng, S. X., & Lu, H. (2014). Nucleostemin stabilizes ARF by inhibiting the ubiquitin ligase ULF. *Oncogene*,

Upregulated expression of nucleolar GTPase nucleostemin (NS) has been associated with increased cellular proliferation potential and tumor malignancy during cancer development. Recent reports attribute the growth regulatory effects of NS protein to its role in facilitating ribosome production. However, the oncogenic potential of NS remains unclear, as imbalanced levels of NS have been reported to exert growth inhibitory effect by modulating p53 tumor-suppressor activity. It also remains in questions if aberrant NS levels might have a p53-independent role in regulation of cell proliferation and growth. In this study, we performed affinity purification and mass spectrometry analysis to explore protein-protein interactions influencing NS growth regulatory properties independently of p53 tumor suppressor. We identified the alternative reading frame (ARF) protein as a key protein associating with NS and further verified the interaction through in vitro and in vivo assays. We demonstrated that NS is

able to regulate cell cycle progression by regulating the stability of the ARF tumor suppressor. Furthermore, overexpression of NS suppressed ARF polyubiquitination by its E3 ligase Ubiquitin Ligase for ARF and elongated its half-life, whereas knockdown of NS led to the decrease of ARF levels. Also, we found that NS can enhance NPM stabilization of ARF. Thus, we propose that in the absence of p53, ARF can be stabilized by NS and nucleophosmin to serve as an alternative tumor-suppressor surveillance, preventing potential cellular transformation resulting from the growth-inducing effects of NS overexpression. *Oncogene* advance online publication, 28 April 2014; doi:10.1038/onc.2014.103.

Lominac, K. D., McKenna, C. L., Schwartz, L. M., Ruiz, P. N., Wroten, M. G., Miller, B. W., et al. (2014). Mesocorticolimbic monoamine correlates of methamphetamine sensitization and motivation. *Frontiers in Systems Neuroscience*, 8, 70.

Methamphetamine (MA) is a highly addictive psychomotor stimulant, with life-time prevalence rates of abuse ranging from 5-10% world-wide. Yet, a paucity of research exists regarding MA addiction vulnerability/resiliency and neurobiological mediators of the transition to addiction that might occur upon repeated low-dose MA exposure, more characteristic of early drug use. As stimulant-elicited neuroplasticity within dopamine neurons innervating the nucleus accumbens (NAC) and prefrontal cortex (PFC) is theorized as central for addiction-related behavioral anomalies, we used a multi-disciplinary research approach in mice to examine the interactions between sub-toxic MA dosing, motivation for MA and mesocorticolimbic monoamines. Biochemical studies of C57BL/6J (B6) mice revealed short- (1 day), as well as longer-term (21 days), changes in extracellular dopamine, DAT and/or D2 receptors during withdrawal from 10, once daily, 2 mg/kg MA injections. Follow-up biochemical studies conducted in mice selectively bred for high vs. low MA drinking (respectively, MAHDR vs. MALDR mice), provided novel support for anomalies in mesocorticolimbic dopamine as a correlate of genetic vulnerability to high MA intake. Finally, neuropharmacological targeting of NAC dopamine in MA-treated B6 mice demonstrated a bi-directional regulation of MA-induced place-conditioning. These results extend extant literature for MA neurotoxicity by demonstrating that even subchronic exposure to relatively low MA doses are sufficient to elicit relatively long-lasting changes in mesocorticolimbic dopamine and that drug-

induced or idiopathic anomalies in mesocorticolimbic dopamine may underpin vulnerability/resiliency to MA addiction.

Lott, D. J., Forbes, S. C., Mathur, S., Germain, S. A., Senesac, C. R., Lee Sweeney, H., et al. (2014).

Assessment of intramuscular lipid and metabolites of the lower leg using magnetic resonance spectroscopy in boys with duchenne muscular dystrophy. *Neuromuscular Disorders : NMD*,

The purpose of this study was to use proton magnetic resonance spectroscopy to assess intramuscular lipid and metabolites of lower leg muscles in boys with Duchenne muscular dystrophy (DMD) and determine its relationship with strength and functional ability.

Spectroscopic measurements were obtained from four muscles of the lower leg in 25 boys with DMD (9.2+/-3.1years) and 10 healthy boys (10.2+/-2.6years). Lipid fractions and metabolite concentrations were also determined. Muscle strength, a timed functional test, and the Modified Brooke Lower Extremity Functional Scale were also determined. Lipid fractions were higher ($p < 0.01$) for the DMD group than healthy subjects for all muscles, and lipid fraction was found to be greater in the older DMD boys. The peroneal muscle demonstrated a significant difference in lipid fraction in all DMD age groups. Lipid fractions in all muscles correlated with functional measures ($r = 0.52-0.70$, $p < 0.001$), with smaller inverse correlations with the strength measure ($r = -0.36$ to -0.56 , $p < 0.05$). These findings provide quantifiable information regarding intramuscular lipid and metabolite levels of different muscles across various age groups in boys with DMD and may be used in determining the effect of interventions in future clinical trials.

Louis, S. G., Barton, J. S., Riha, G. M., Orloff, S. L., Sheppard, B. C., Pommier, R. F., et al. (2014).

The international normalized ratio overestimates coagulopathy in patients after major hepatectomy. *American Journal of Surgery*, 207(5), 723-727.

BACKGROUND: The International Normalized Ratio (INR) is commonly used to guide therapy after hepatectomy. We hypothesized that the use of thrombelastography (TEG) would demonstrate a decreased incidence of hypocoagulability in this patient population. METHODS: Seventy-eight patients were prospectively enrolled before undergoing hepatectomy. INR, TEG, and coagulation factors were drawn before incision, postoperatively, and on postoperative days 1, 3, and 5. RESULTS: Patients demonstrated an elevated INR at all postoperative time points.

However, TEG demonstrated a decreased R value postoperatively, with subsequent normalization. Other TEG measurements were equivalent to preoperative values. All procoagulant factors save factor VIII decreased postoperatively, with a simultaneous decrease in protein C. CONCLUSIONS: TEG demonstrated a brief hypercoagulable state after major hepatectomy, with coagulation subsequently normalizing. The INR significantly overestimates hypocoagulability after hepatectomy and these data call into question current practices using the INR to guide therapy in this patient population.

Ma, J., Prince, A. L., Bader, D., Hu, M., Ganu, R., Baquero, K., et al. (2014). High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. *Nature Communications*, 5, 3889.

The intestinal microbiome is a unique ecosystem and an essential mediator of metabolism and obesity in mammals. However, studies investigating the impact of the diet on the establishment of the gut microbiome early in life are generally lacking, and most notably so in primate models. Here we report that a high-fat maternal or postnatal diet, but not obesity per se, structures the offspring's intestinal microbiome in *Macaca fuscata* (Japanese macaque). The resultant microbial dysbiosis is only partially corrected by a low-fat, control diet after weaning. Unexpectedly, early exposure to a high-fat diet diminished the abundance of non-pathogenic *Campylobacter* in the juvenile gut, suggesting a potential role for dietary fat in shaping commensal microbial communities in primates. Our data challenge the concept of an obesity-causing gut microbiome and rather provide evidence for a contribution of the maternal diet in establishing the microbiota, which in turn affects intestinal maintenance of metabolic health.

MacArthur, C. J., Wilmot, B., Wang, L., Schuller, M., Lighthall, J., & Trune, D. (2014). Genetic susceptibility to chronic otitis media with effusion: Candidate gene single nucleotide polymorphisms. *Laryngoscope*, 124(5), 1229-1235.

Objectives/Hypothesis The genetic factors leading to a predisposition to otitis media are not well understood. The objective of the current study was to develop a tag-single nucleotide polymorphism (SNP) panel to determine if there is an association between candidate gene polymorphisms and the development of chronic otitis media with effusion. Study Design A 1:1

case/control design of 100 cases and 100 controls was used. The study was limited to the chronic otitis media with effusion phenotype to increase the population homogeneity. Methods A panel of 192 tag-SNPs was selected. Saliva for DNA extraction was collected from 100 chronic otitis media with effusion cases and 100 controls. After quality control, 100 case and 79 control samples were available for hybridization. Genomic DNA from each subject was hybridized to the SNP probes, and genotypes were generated. Quality control across all samples and SNPs reduced the final SNPs used for analysis to 170. Each SNP was then analyzed for statistical association with chronic otitis media with effusion. Results Eight SNPs from four genes had an unadjusted P value of $<.05$ for association with the chronic otitis media with effusion phenotype (TLR4, MUC5B, SMAD2, SMAD4); five of these polymorphisms were in the TLR4 gene. Conclusions Even though these results need to be replicated in a novel population, the presence of five SNPs in the TLR4 gene having association with chronic otitis media with effusion in our study population lends evidence for the possible role of this gene in the susceptibility to otitis media. © 2013 The American Laryngological, Rhinological and Otological Society, Inc.

Maki, E., Oh, K., Rogers, S., & Sohaey, R. (2014). Imaging and differential diagnosis of suprarenal masses in the fetus. *Journal of Ultrasound in Medicine : Official Journal of the American Institute of Ultrasound in Medicine*, 33(5), 895-904.

Prenatal sonography and magnetic resonance imaging of suprarenal fetal masses is presented, along with clinical information and follow-up. Imaging pearls and differential considerations for each diagnosis will be discussed. Fetal suprarenal mass diagnoses include neuroblastoma, extralobar pulmonary sequestration, congenital adrenal hyperplasia, partial multicystic dysplastic kidney, renal duplication, urinoma, gastric duplication cyst, and splenic cyst. Recognizing the range of malignant and benign suprarenal fetal masses that can present on prenatal imaging can help guide patient counseling and management.

Malouli, D., Hansen, S. G., Nakayasu, E. S., Marshall, E. E., Hughes, C. M., Ventura, A. B., et al. (2014). Cytomegalovirus pp65 limits dissemination but is dispensable for persistence. *Journal of Clinical Investigation*, 124(5), 1928-1944.

The most abundantly produced virion protein in human cytomegalovirus (HCMV) is the

immunodominant phosphoprotein 65 (pp65), which is frequently included in CMV vaccines. Although it is nonessential for in vitro CMV growth, pp65 displays immunomodulatory functions that support a potential role in primary and/or persistent infection. To determine the contribution of pp65 to CMV infection and immunity, we generated a rhesus CMV lacking both pp65 orthologs (RhCMV pp65ab). While deletion of pp65ab slightly reduced growth in vitro and increased defective particle formation, the protein composition of secreted virions was largely unchanged. Interestingly, pp65 was not required for primary and persistent infection in animals. Immune responses induced by RhCMV Δ pp65ab did not prevent reinfection with rhesus CMV; however, reinfection with RhCMV Δ US2-11, which lacks viral-encoded MHC-I antigen presentation inhibitors, was prevented. Unexpectedly, induction of pp65b-specific T cells alone did not protect against RhCMV Δ US2-11 challenge, suggesting that T cells targeting multiple CMV antigens are required for protection. However, pp65-specific immunity was crucial for controlling viral dissemination during primary infection, as indicated by the marked increase of RhCMV Δ pp65ab genome copies in CMV-naive, but not CMV-immune, animals. Our data provide rationale for inclusion of pp65 into CMV vaccines but also demonstrate that pp65-induced T cell responses alone do not recapitulate the protective effect of natural infection.

Maly, A. G., Steel, T. L., Fu, R., Lieberman, D. A., & Becker, T. M. (2014). Colorectal cancer screening among American Indians in a Pacific Northwest tribe: Cowlitz tribal BRFSS project, 2009-2010. *Public Health Reports (Washington, D.C.: 1974)*, 129(3), 280-288.

OBJECTIVES: Colorectal cancer (CRC) screening is low among American Indians (AIs). We describe the demographics, health status, prevalence of modifiable CRC risk factors, and use of CRC screening modalities in a Pacific Northwest AI tribe. **METHODS:** We conducted a survey among Cowlitz tribal members using a Behavioral Risk Factor Surveillance System (BRFSS) questionnaire. We analyzed demographic, health status, behavioral risk factor, and CRC screening variables. Using the Washington State 2010 BRFSS, we compared tribal members with non-Hispanic white (NHW) people. We used logistic regression to examine factors associated with CRC screening for tribal members. **RESULTS:** A greater proportion of tribal members than NHW people reported living below the federal poverty level (12% vs. 7%, $p=0.013$). A greater proportion of tribal members than NHW people aged ≥ 50 years had poor self-reported health

(27% vs. 16%, $p=0.006$) and were without health insurance (12% vs. 6%, $p=0.004$). A greater proportion of tribal members than NHW people had a fecal occult blood test within the past year (20% vs. 13%, $p=0.006$). Being 60-69 years of age (odds ratio [OR] = 2.6, 95% confidence interval [CI] 1.4, 4.9), ≥ 70 years of age (OR=2.2, 95% CI 1.1, 4.5), and having a personal health-care provider (OR=3.7, 95% CI 1.4, 9.6) were associated with increased screening adherence in tribal members. CONCLUSION: Data from the Cowlitz Tribal BRFSS demonstrate that members are receiving CRC screening in the same proportions as NHW people despite lower sociodemographic and health status indicators among members. Unique characteristics of the tribe likely contribute to this finding.

Marshall, N. E., Vanderhoeven, J., Eden, K. B., Segel, S. Y., & Guise, J. M. (2014). Impact of simulation and team training on postpartum hemorrhage management in non-academic centers. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, , 1-20.

Abstract Objective: Prompt recognition and response to post-partum hemorrhage (PPH) are vital in preventing maternal morbidity and mortality. We conducted a multi-center study to evaluate in situ simulation and team training for PPH among experienced clinical teams in non-academic hospitals in urban and rural communities. Methods: A longitudinal intervention study was performed in 6 Oregon community hospitals. All teams responded to an in situ simulated delivery and postpartum hemorrhage using trained actors and an obstetric birthing simulator, followed by a debriefing and training session. The simulation scenario was then repeated in 9-12 months. All sessions were digitally video recorded and independently reviewed by two obstetricians using a structured evaluation form. PPH management including clinical response times were compared before and after team training using Student paired t-test and McNemar's test. Results: Twenty-two teams completed paired case simulations. Team training significantly improved response times in the management of PPH, including the recognition of PPH, time to administer first medication, performance of uterine massage, and time to administer second medication. Medical management (use of 3 indicated medications) improved after training from 27.3% to 63.6%,

p=0.01. Conclusions: Simulation and team training significantly improved postpartum hemorrhage response times among clinically-experienced community labor and delivery teams.

Martin, B. I., Lurie, J. D., Tosteson, A. N. A., Deyo, R. A., Tosteson, T. D., Weinstein, J. N., et al.

(2014). Indications for spine surgery: Validation of an administrative coding algorithm to classify degenerative diagnoses. *Spine*, 39(9), 769-779.

Study Design: Retrospective analysis of Medicare claims linked to a multicenter clinical trial.

Objective: The Spine Patient Outcomes Research Trial (SPORT) provided a unique opportunity to examine the validity of a claims-based algorithm for grouping patients by surgical indication.

SPORT enrolled patients for lumbar disc herniation, spinal stenosis, and degenerative spondylolisthesis. We compared the surgical indication derived from Medicare claims with that provided by SPORT surgeons, the "gold standard." Summary of Background Data: Administrative data are frequently used to report procedure rates, surgical safety outcomes, and costs in the management of spinal surgery. However, the accuracy of using diagnosis codes to classify patients by surgical indication has not been examined. Methods: Medicare claims were link to beneficiaries enrolled in SPORT. The sensitivity and specificity of 3 claims-based approaches to group patients on the basis of surgical indications were examined: (1) using the first listed diagnosis; (2) using all diagnoses independently; and (3) using a diagnosis hierarchy on the basis of the support for fusion surgery. Results: Medicare claims were obtained from 376 SPORT participants, including 21 with disc herniation, 183 with spinal stenosis, and 172 with degenerative spondylolisthesis. The hierarchical coding algorithm was the most accurate approach for classifying patients by surgical indication, with sensitivities of 76.2%, 88.1%, and 84.3% for disc herniation, spinal stenosis, and degenerative spondylolisthesis cohorts, respectively. The specificity was 98.3% for disc herniation, 83.2% for spinal stenosis, and 90.7% for degenerative spondylolisthesis. Misclassifications were primarily due to codes attributing more complex pathology to the case. Conclusion: Standardized approaches for using claims data to group patients accurately by surgical indications have widespread interest. We found that a hierarchical coding approach correctly classified more than 90% of spine patients into their respective SPORT cohorts. Therefore, claims data seem to be a reasonably valid approach to classifying patients by surgical indication. © 2014, Lippincott Williams & Wilkins.

Martin, L. D., Dissen, G. A., McPike, M. J., & Brambrink, A. M. (2014). Effects of anesthesia with isoflurane, ketamine, or propofol on physiologic parameters in neonatal rhesus macaques (*macaca mulatta*). *Journal of the American Association for Laboratory Animal Science : JAALAS*, 53(3), 290-300.

Isoflurane, ketamine, and propofol are common anesthetics in human and nonhuman primate medicine. However, scant normative data exist regarding the response of neonatal macaques to these anesthetics. We compared the effects of isoflurane, ketamine, and propofol anesthesia on physiologic parameters in neonatal rhesus macaques. Neonatal rhesus macaques (age, 5 to 7 d) were exposed to isoflurane (n = 5), ketamine (n = 4), propofol (n = 4) or no anesthesia (n = 5) for 5 h. The anesthetics were titrated to achieve a moderate anesthetic plane, and heart rate, blood pressure, respiratory rate, end tidal carbon dioxide, oxygen saturation, and temperature were measured every 15 min. Venous blood samples were collected to determine blood gases and metabolic status at baseline, 0.5, 2.5, and 4.5 h after induction and at 3 h after the end of anesthesia. Compared with ketamine, isoflurane caused more hypotensive events and necessitated the administration of increased volumes of intravenous fluids to support blood pressure throughout anesthesia; no significant differences were observed between the isoflurane and propofol groups for these parameters. In addition, isoflurane resulted in a significantly shorter average time to extubation, compared with both ketamine and propofol. Due to supportive care, other physiologic variables remained stable between anesthetic regimens and throughout the 5-h exposure. These data improve our understanding of the effects of these 3 anesthetics in neonatal rhesus macaques and will aid veterinarians and researchers as they consider the risks and benefits of and resources required during general anesthesia in these animals.

Massarwa, A., Caughey, A. B., & Lee, V. (2014). The effect of mode of delivery on neonatal outcomes in myelomeningocele. *Obstetrics and Gynecology*, 123 Suppl 1, 155S.

INTRODUCTION: The question of the optimal route of delivery for pregnancies complicated by myelomeningocele is still controversial. The purpose of this study was to evaluate the relationship between mode of delivery and neonatal outcomes in such cases. METHODS: Retrospective cohort study of singleton pregnancies complicated by myelomeningocele in a database of linked vital

statistics and hospital discharge data in California between 2005 and 2008. Outcomes examined included neonatal death, respiratory distress syndrome, transient tachypnea of the newborn, intraventricular hemorrhage, necrotizing enterocolitis, meningitis, and infant death. Neonatal outcomes were compared using the chi test and Fisher's exact test for statistical analysis.

RESULTS: Five hundred seven patients were eligible for the study. There were no significant differences in neonatal death, infant death, respiratory distress syndrome, or meningitis between neonates delivered by cesarean delivery compared with those delivered vaginally. Cesarean delivery was associated with significantly higher rates of transient tachypnea of the newborn (6.6% compared with 2.1%, $P=.032$) and intraventricular hemorrhage (2.5% compared with 0%, $P=.029$) compared with vaginal delivery. CONCLUSIONS: In pregnancies complicated by myelomeningocele, mode of delivery does not significantly affect perinatal outcomes.

Matsui, A., Jarvie, B. C., Robinson, B. G., Hentges, S. T., & Williams, J. T. (2014). Separate GABA afferents to dopamine neurons mediate acute action of opioids, development of tolerance, and expression of withdrawal. *Neuron*, GABA release from interneurons in VTA, projections from the nucleus accumbens (NAc), and rostromedial tegmental nucleus (RMTg) was selectively activated in rat brain slices. The inhibition induced by mu-opioid agonists was pathway dependent. Morphine induced a 46% inhibition of IPSCs evoked from the RMTg, 18% from NAc, and IPSCs evoked from VTA interneurons were almost insensitive (11% inhibition). In vivo morphine treatment resulted in tolerance to the inhibition of RMTg, but not local interneurons or NAc, inputs. One common sign of opioid withdrawal is an increase in adenosine-dependent inhibition. IPSCs evoked from the NAc were potently inhibited by activation of presynaptic adenosine receptors, whereas IPSCs evoked from RMTg were not changed. Blockade of adenosine receptors selectively increased IPSCs evoked from the NAc during morphine withdrawal. Thus, the acute action of opioids, the development of tolerance, and the expression of withdrawal are mediated by separate GABA afferents to dopamine neurons.

Maytin, M., Wilkoff, B. L., Brunner, M., Cronin, E., Love, C. J., Grazia Bongiorno, M., et al. (2014).

Multicenter experience with extraction of the Riata/Riata ST ICD lead. *Heart Rhythm : The Official*

Journal of the Heart Rhythm Society,

BACKGROUND: In November 2011, the FDA issued a Class I Recall of Riata and Riata ST ICD leads. Management recommendations regarding the recall have remained controversial.

OBJECTIVE: Data regarding the safety and feasibility of extraction of Riata ICD leads are limited.

METHODS: We performed a retrospective study of patients undergoing extraction of Riata/ST

leads at 11 centers. **RESULTS:** Between July 2003-April 2013, 577 Riata/ST leads were extracted from 577 patients (Riata 84%, Riata ST 16%). Complete procedural success achieved in 99.1%.

Cohort was 78% male with mean age 60 years and mean LVEF of 34+/-14%. Average implant duration was 44.7 months (range, 0-124.6). The majority of leads extracted were for infection (53.0%); 35.7% for lead malfunction. Evaluation for lead integrity was performed in 295 cases.

Of these, 34.9% were found to have externalized cables. Implant duration was significantly longer in leads with externalized cables ($p < 0.0001$). No difference in lead integrity was noted between Riata and Riata ST (11.7% v. 17.7% failure, $p = 0.23$). Among leads in which cable externalization was noted, laser sheaths were employed more frequently ($p = 0.01$). Major complications included 3 SVC/RV perforations requiring surgical intervention with one death 12 days post-procedure and 1 pericardial effusion requiring percutaneous drainage (0.87%).

CONCLUSION: Extraction of the Riata/ST leads can be challenging and leads with externalized cables may require specific extraction techniques. Extraction of the Riata/ST leads can be performed safely by experienced operators at high-volume centers with a complication rate comparable to published data.

McCarthy, M. J., & Lyons, K. S. (2014). Incongruence between stroke survivor and spouse perceptions of survivor functioning and effects on spouse mental health: A mixed-methods pilot study. *Aging and Mental Health,*

Objectives: This pilot study investigated stroke survivors' and caregiving spouses' individual perspectives on survivor cognitive and physical functioning and the extent to which incongruence between partners' perceptions affects spouse depressive symptoms and overall mental health. **Method:** Mixed-methods, with quantitative survey data from 35 couples and qualitative interview data from a subsample of 13 couples being collected and analyzed using paired t-tests, multiple regression with survivor-spouse discrepancy scores as predictors of spouse depressive

symptoms, and interpretive-description techniques. Results: Quantitative data indicated that spouses rated survivor cognitive functioning as significantly worse than survivors rated their own and that survivor-spouse discrepancy scores for physical functioning were significantly associated with spouse depressive symptoms. Qualitative data enhanced understanding about the nuances of partner incongruence and the ramifications of partner incongruence for spouse mental health. Conclusion: Partner incongruence has an impact on spouse depressive symptoms and overall mental health. Interventions targeted at survivor-spouse dyads and focused on improving communication between partners about survivor abilities may be effective for improving the mental health of spousal caregivers. © 2014 © 2014 Taylor & Francis.

McEvoy, C. T., Schilling, D., Clay, N., Jackson, K., Go, M. D., Spitale, P., et al. (2014). Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: A randomized clinical trial. *JAMA : The Journal of the American Medical Association*, 311(20), 2074-2082.

IMPORTANCE: Maternal smoking during pregnancy adversely affects offspring lung development, with lifelong decreases in pulmonary function and increased asthma risk. In a primate model, vitamin C blocked some of the in-utero effects of nicotine on lung development and offspring pulmonary function. **OBJECTIVE:** To determine if newborns of pregnant smokers randomized to receive daily vitamin C would have improved results of pulmonary function tests (PFTs) and decreased wheezing compared with those randomized to placebo. **DESIGN, SETTING, AND PARTICIPANTS:** Randomized, double-blind trial conducted in 3 sites in the Pacific Northwest between March 2007 and January 2011. One hundred fifty-nine newborns of randomized pregnant smokers (76 vitamin C treated and 83 placebo treated) and 76 newborns of pregnant nonsmokers were studied with newborn PFTs. Follow-up assessment including wheezing was assessed through age 1 year, and PFTs were performed at age 1 year. **INTERVENTIONS:** Pregnant women were randomized to receive vitamin C (500 mg/d) (n = 89) or placebo (n = 90). **MAIN OUTCOMES AND MEASURES:** The primary outcome was measurement of newborn pulmonary function (ratio of the time to peak tidal expiratory flow to expiratory time [TPTEF:TE] and passive respiratory compliance per kilogram [Cr_s/kg]) within 72 hours of age. Secondary outcomes included incidence of wheezing through age 1 year and PFT results at age 1 year. A

subgroup of pregnant smokers and nonsmokers had genotyping performed. RESULTS: Newborns of women randomized to vitamin C (n = 76), compared with those randomized to placebo (n = 83), had improved pulmonary function as measured by TPTEF:TE (0.383 vs 0.345 [adjusted 95% CI for difference, 0.011-0.062]; P = .006) and Crs/kg (1.32 vs 1.20 mL/cm H₂O/kg [95% CI, 0.02-0.20]; P = .01). Offspring of women randomized to vitamin C had significantly decreased wheezing through age 1 year (15/70 [21%] vs 31/77 [40%]; relative risk, 0.56 [95% CI, 0.33-0.95]; P = .03). There were no significant differences in the 1-year PFT results between the vitamin C and placebo groups. The effect of maternal smoking on newborn lung function was associated with maternal genotype for the alpha5 nicotinic receptor (rs16969968) (P < .001 for interaction). CONCLUSIONS AND RELEVANCE: Supplemental vitamin C taken by pregnant smokers improved newborn PFT results and decreased wheezing through 1 year in the offspring. Vitamin C in pregnant smokers may be an inexpensive and simple approach to decrease the effects of smoking in pregnancy on newborn pulmonary function and respiratory morbidities. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00632476.

Mesgarani, N., David, S. V., Fritz, J. B., & Shamma, S. A. (2014). Mechanisms of noise robust representation of speech in primary auditory cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 111(18), 6792-6797.

Humans and animals can reliably perceive behaviorally relevant sounds in noisy and reverberant environments, yet the neural mechanisms behind this phenomenon are largely unknown. To understand how neural circuits represent degraded auditory stimuli with additive and reverberant distortions, we compared single-neuron responses in ferret primary auditory cortex to speech and vocalizations in four conditions: clean, additive white and pink (1/f) noise, and reverberation. Despite substantial distortion, responses of neurons to the vocalization signal remained stable, maintaining the same statistical distribution in all conditions. Stimulus spectrograms reconstructed from population responses to the distorted stimuli resembled more the original clean than the distorted signals. To explore mechanisms contributing to this robustness, we simulated neural responses using several spectrotemporal receptive field models that incorporated either a static nonlinearity or subtractive synaptic depression and multiplicative gain normalization. The static model failed to suppress the distortions. A dynamic model incorporating

feedforward synaptic depression could account for the reduction of additive noise, but only the combined model with feedback gain normalization was able to predict the effects across both additive and reverberant conditions. Thus, both mechanisms can contribute to the abilities of humans and animals to extract relevant sounds in diverse noisy environments.

Messenger, W. B., Campbell, J. P., Faridi, A., Shippey, L., Bailey, S. T., Lauer, A. K., et al. (2014).

Injection frequency and anatomic outcomes 1 year following conversion to aflibercept in patients with neovascular age-related macular degeneration. *The British Journal of Ophthalmology*,

BACKGROUND/AIM: To evaluate the clinical, anatomic and functional effects of conversion to aflibercept following ranibizumab and/or bevacizumab in patients with neovascular age-related macular degeneration (AMD). METHODS: A retrospective review of patients with neovascular AMD treated with intravitreal ranibizumab and/or bevacizumab who were switched to aflibercept was performed. The primary outcome was change in injection frequency in the year following the change. Secondary outcomes included change in central macular thickness (CMT) at 6 months and 1 year, presence of intraretinal and subretinal fluid at 6 months and visual acuity at 1 year.

RESULTS: A total of 109 eyes with neovascular AMD were switched to aflibercept and met inclusion criteria. Overall, aflibercept injection frequency was unchanged with patients receiving 7.4 anti-vascular endothelial growth factor (VEGF) injections the year prior to conversion compared with 7.2 aflibercept injections in the year following ($p=0.47$). However, the change to aflibercept was associated with improvement in CMT from 324 to 295 μm ($p=0.0001$) at 6 months and 299 μm ($p=0.0047$) at 1 year. There was no effect on visual acuity at 1 year. In a subgroup analysis, patients who had received ≥ 10 anti-VEGF injections in the year prior had fewer injections (11.1 to 8.4, $p<0.0001$) and clinic visits (13.9 to 9.6, $p<0.0001$) as well as a significant decrease in CMT (-35 μm , $p=0.02$). CONCLUSIONS: In our population, switching to aflibercept therapy was not associated with a change in injection frequency nor improved visual acuity, but was associated with improved CMT at 6 months and 1 year. In patients who received at least 10 anti-VEGF injections in the year prior, transitioning to aflibercept was associated with a reduced injection frequency and CMT, suggesting potential cost savings in this population.

Meza-Romero, R., Benedek, G., Yu, X., Mooney, J. L., Dahan, R., Duvshani, N., et al. (2014). HLA-DR α 1 constructs block CD74 expression and MIF effects in experimental autoimmune encephalomyelitis. *Journal of Immunology*, 192(9), 4164-4173.

CD74, the cell-surface form of the MHC class II invariant chain, is a key inflammatory factor that is involved in various immunemediated diseases as part of the macrophage migration inhibitory factor (MIF) binding complex. However, little is known about the natural regulators of CD74 in this context. In order to study the role of the HLA-DR molecule in regulating CD74, we used the HLADRa1 domain, which was shown to bind to and downregulate CD74 on CD11b⁺ monocytes. We found that DR α 1 directly inhibited binding of MIF to CD74 and blocked its downstream inflammatory effects in the spinal cord of mice with experimental autoimmune encephalomyelitis (EAE). Potency of the DR α 1 domain could be destroyed by trypsin digestion but enhanced by addition of a peptide extension (myelin oligodendrocyte glycoprotein [MOG]-35-55 peptide) that provided secondary structure not present in DR α 1. These data suggest a conformationally sensitive determinant on DR α 1-MOG that is responsible for optimal binding to CD74 and antagonism of MIF effects, resulting in reduced axonal damage and reversal of ongoing clinical and histological signs of EAE. These results demonstrate natural antagonist activity of DR α 1 for MIF that was strongly potentiated by the MOG peptide extension, resulting in a novel therapeutic, DR α 1-MOG-35-55, that within the limitations of the EAE model may have the potential to treat autoimmune diseases such as multiple sclerosis. *The Journal of Immunology*, 2014, 192: 4164-4173. © 2014 by The American Association of Immunologists, Inc.

Micks, E. A., Jensen, J. T., & Bednarek, P. H. (2014). The effect of nitroglycerin on the IUD insertion experience in nulliparous women: A pilot study. *Contraception*,

OBJECTIVE: Concern about pain during placement of an intrauterine device (IUD) represents a barrier to use, especially among nulliparous women. We hypothesized that nitroglycerin gel applied vaginally 30 min prior to IUD placement would reduce insertion-related pain. STUDY DESIGN: We designed a randomized, double-blinded, placebo-controlled pilot study to evaluate the efficacy and tolerability of 0.5-mg nitroglycerin gel (1 mL) or identical placebo gel applied vaginally in nulliparous women 30 min prior to IUD placement. The study was limited to women who opted for the levonorgestrel-releasing intrauterine system. Subjects completed a series of

100-mm visual analogue scales at several time points. The primary outcome was subject-reported pain with passage of the IUD through the cervix. Secondary outcomes included subject-reported pain at other time points, provider-reported ease of insertion, side effects, adverse events and need for additional dilation. RESULTS: A total of 24 women were randomized. Baseline characteristics were similar between groups. The mean pain score with IUD deployment was 55.0 mm [standard deviation (SD) = 29.7 mm] in the placebo group and 57.4 mm (SD 22.1 mm) in the nitroglycerin group ($p=.82$). There was no difference in ease of insertion reported by providers. Two subjects required dilation, one in each group. CONCLUSION: Vaginal administration of 0.5-mg nitroglycerin gel 30 min prior to IUD placement does not appear to decrease patient-reported procedural pain among nulliparous women or ease of insertion for providers.

Miller, L. D., Gardiner, S. K., & Gubler, K. D. (2014). Emergency department referral for organ donation: More organ donors and more organs per donor. *American Journal of Surgery*, 207(5), 728-734.

BACKGROUND: This study sought to determine whether early referral from the emergency department (ED) would increase the number of organ donors and the number of organs transplanted per donor (OTPD). METHODS: This is a retrospective cohort analysis of all patients referred to a single organ procurement organization for a period of 60 months. RESULTS: Patients referred for organ donation evaluation from the ED were more likely to become organ donors than patients referred from the intensive care unit (19.3% vs 5.2%, $P < .001$). ED referrals had a greater number of OTPD than those referred from the intensive care unit (mean 3.79 vs 3.16, $P = .024$), even after adjusting for the higher proportion of ED referrals who were trauma patients ($P = .001$). CONCLUSIONS: Referral for organ donation from the ED is associated with an increased likelihood of organ recovery and with an increased number of OTPD.

Mist, S., & Jones, K. (2014). Mindfulness in a fibromyalgia population. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A94-5.

Mitalipov, S., Amato, P., Parry, S., & Falk, M. J. (2014). Limitations of preimplantation genetic diagnosis for mitochondrial DNA diseases. *Cell Reports*, 7(4), 935-937.

Mitalipov, S., & Wolf, D. (2009). Totipotency, pluripotency and nuclear reprogramming. *Advances in Biochemical Engineering/Biotechnology*, 114, 185-199.

Mammalian development commences with the totipotent zygote which is capable of developing into all the specialized cells that make up the adult animal. As development unfolds, cells of the early embryo proliferate and differentiate into the first two lineages, the pluripotent inner cell mass and the trophoblast. Pluripotent cells can be isolated, adapted and propagated indefinitely in vitro in an undifferentiated state as embryonic stem cells (ESCs). ESCs retain their ability to differentiate into cells representing the three major germ layers: endoderm, mesoderm or ectoderm or any of the 200+ cell types present in the adult body. Since many human diseases result from defects in a single cell type, pluripotent human ESCs represent an unlimited source of any cell or tissue type for replacement therapy thus providing a possible cure for many devastating conditions. Pluripotent cells resembling ESCs can also be derived experimentally by the nuclear reprogramming of somatic cells. Reprogrammed somatic cells may have an even more important role in cell replacement therapies since the patient's own somatic cells can be used for reprogramming thereby eliminating immune based rejection of transplanted cells. In this review, we summarize two major approaches to reprogramming: (1) somatic cell nuclear transfer and (2) direct reprogramming using genetic manipulations.

Moal, B., Schwab, F., Ames, C. P., Smith, J. S., Ryan, D., Mummaneni, P. V., et al. (2014).

Radiographic outcomes of adult spinal deformity correction: A critical analysis of variability and failures across deformity patterns. *Spine Deformity*, 2(3), 219-225.

Study Design Multicenter, prospective, consecutive, surgical case series from the International Spine Study Group. Objectives To evaluate the effectiveness of surgical treatment in restoring spinopelvic (SP) alignment. Summary of Background Data Pain and disability in the setting of adult spinal deformity have been correlated with global coronal alignment (GCA), sagittal vertical axis (SVA), pelvic incidence/lumbar lordosis mismatch (PI-LL), and pelvic tilt (PT). One of the main goals of surgery for adult spinal deformity is to correct these parameters to restore harmonious SP alignment. Methods Inclusion criteria were operative patients (age greater than 18 years) with baseline (BL) and 1-year full-length X-rays. Thoracic and thoracolumbar Cobb angle and previous mentioned parameters were calculated. Each parameter at BL and 1 year was

categorized as either pathological or normal. Pathologic limits were: Cobb greater than 30°, GCA greater than 40 mm, SVA greater than 40 mm, PI-LL greater than 10°, and PT greater than 20°. According to thresholds, corrected or worsened alignment groups of patients were identified and overall radiographic effectiveness of procedure was evaluated by combining the results from the coronal and sagittal planes. Results A total of 161 patients (age, 55 ± 15 years) were included. At BL, 80% of patients had a Cobb angle greater than 30°, 25% had a GCA greater than 40 mm, and 42% to 58% had a pathological sagittal parameter of PI-LL, SVA, and/or PT. Sagittal deformity was corrected in about 50% of cases for patients with pathological SVA or PI-LL, whereas PT was most commonly worsened (24%) and least often corrected (24%). Only 23% of patients experienced complete radiographic correction of the deformity. Conclusions The frequency of inadequate SP correction was high. Pelvic tilt was the parameter least likely to be well corrected. The high rate of SP alignment failure emphasizes the need for better preoperative planning and intraoperative imaging. © 2014 Scoliosis Research Society.

Mountz, J. M., Yankeelov, T. E., Rubin, D. L., Buatti, J. M., Erikson, B. J., Fennessy, F. M., et al. (2014). Letter to cancer center directors: Progress in quantitative imaging as a means to predict and/or measure tumor response in cancer therapy trials. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*,

Nabavizadeh, N., Simeonova, A. O., Waller, J. G., Romer, J. L., Monaco, D. L., Elliott, D. A., et al. (2014). Volumetric-modulated arc radiotherapy for pancreatic malignancies: Dosimetric comparison with sliding-window intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy. *Medical Dosimetry : Official Journal of the American Association of Medical Dosimetrists*,

Volumetric-modulated arc radiotherapy (VMAT) is an iteration of intensity-modulated radiotherapy (IMRT), both of which deliver highly conformal dose distributions. Studies have shown the superiority of VMAT and IMRT in comparison with 3-dimensional conformal radiotherapy (3D-CRT) in planning target volume (PTV) coverage and organs-at-risk (OARs) sparing. This is the first study examining the benefits of VMAT in pancreatic cancer for doses more than 55.8Gy. A planning study comparing 3D-CRT, IMRT, and VMAT was performed in 20

patients with pancreatic cancer. Treatments were planned for a 25-fraction delivery of 45Gy to a large field followed by a reduced-volume 8-fraction external beam boost to 59.4Gy in total. OARs and PTV doses, conformality index (CI) deviations from 1.0, monitor units (MUs) delivered, and isodose volumes were compared. IMRT and VMAT CI deviations from 1.0 for the large-field and the boost plans were equivalent (large field: 0.032 and 0.046, respectively; boost: 0.042 and 0.037, respectively; $p > 0.05$ for all comparisons). Both IMRT and VMAT CI deviations from 1.0 were statistically superior to 3D-CRT (large field: 0.217, boost: 0.177; $p < 0.05$ for all comparisons). VMAT showed reduction of the mean dose to the boost PTV (VMAT: 61.4Gy, IMRT: 62.4Gy, and 3D-CRT: 62.3Gy; $p < 0.05$). The mean number of MUs per fraction was significantly lower for VMAT for both the large-field and the boost plans. VMAT delivery time was less than 3 minutes compared with 8 minutes for IMRT. Although no statistically significant dose reduction to the OARs was identified when comparing VMAT with IMRT, VMAT showed a reduction in the volumes of the 100% isodose line for the large-field plans. Dose escalation to 59.4Gy in pancreatic cancer is dosimetrically feasible with shorter treatment times, fewer MUs delivered, and comparable CIs for VMAT when compared with IMRT.

Narang, N., Thibodeau, J. T., Levine, B. D., Gore, M. O., Ayers, C. R., Lange, R. A., et al. (2014).

Inaccuracy of estimated resting oxygen uptake in the clinical setting. *Circulation*, 129(2), 203-210.

BACKGROUND: The Fick principle (cardiac output = oxygen uptake ($\dot{V}O_2$)/systemic arterio-venous oxygen difference) is used to determine cardiac output in numerous clinical situations. However, estimated rather than measured $\dot{V}O_2$ is commonly used because of complexities of the measurement, though the accuracy of estimation remains uncertain in contemporary clinical practice. METHODS AND RESULTS: From 1996 to 2005, resting $\dot{V}O_2$ was measured via the Douglas bag technique in adult patients undergoing right heart catheterization. Resting $\dot{V}O_2$ was estimated by each of 3 published formulae. Agreement between measured and estimated $\dot{V}O_2$ was assessed overall, and across strata of body mass index, sex, and age. The study included 535 patients, with mean age 55 yrs, mean body mass index 28.4 kg/m²; 53% women; 64% non-white. Mean (+/-standard deviation) measured $\dot{V}O_2$ was 241 +/- 57 ml/min. Measured $\dot{V}O_2$ differed significantly from values derived from all 3 formulae, with median (interquartile range) absolute

differences of 28.4 (13.1, 50.2) ml/min, 37.7 (19.4, 63.3) ml/min, and 31.7 (14.4, 54.5) ml/min, for the formulae of Dehmer, LaFarge, and Bergstra, respectively (P25% in 17% to 25% of patients depending on the formula used. Median absolute differences were greater in severely obese patients (body mass index > 40 kg/m²), but were not affected by sex or age.

CONCLUSIONS: Estimates of resting O₂ derived from conventional formulae are inaccurate, especially in severely obese individuals. When accurate hemodynamic assessment is important for clinical decision-making, O₂ should be directly measured.

Naugler, W. E. (2014). Bile acid flux is necessary for normal liver regeneration. *PLoS One*, 9(5), e97426.

BACKGROUND & AIMS: Many signals governing liver regeneration (LR) following 2/3 partial hepatectomy (PH) are recognized, but the primary signal(s) remains unknown. The aim of the study was to confirm that the remnant liver after PH lacks capacity to secrete the BA pool returning via the enterohepatic circulation (EHC), which may in turn stimulate LR. METHODS: After standard PH, BA flux was documented and BA signaling (Fgf15) and synthesis (Cyp7a) determined by qPCR. Rat biliary fistula (BF) and Asbt knockout mouse models interrupted the EHC prior to PH, and standard assays for LR employed along with complete RNA sequencing. CCl₄ intoxication after BF tested the hypothesis in an alternate injury model. RESULTS: BA rise in systemic blood immediately following PH, confirming that the remnant liver cannot handle the BA returning via portal circulation. When the BA pool is drained prior to PH in the rat BF model, LR is markedly attenuated, a phenomenon reversed with duodenal BA replacement. Hepatocyte proliferation is similarly attenuated after PH in the Asbt knockout mouse as well as after CCl₄ intoxication in rats with BF. Complete RNA sequencing in the rat PH model shows that early c-jun and AP-1 gene expression pathways are down regulated in the absence of BA, coincident with attenuated LR. CONCLUSIONS: Absent BA return to the liver after PH or CCl₄ injury markedly attenuates LR, though hepatocyte proliferation still occurs, inferring that BA flux and signaling are not the sole signals governing LR. Transcriptional networks involving c-jun and AP-1 are involved in the BA-specific effects on hepatocyte proliferation.

Ng, J. K., Stout, A. U., Aaby, A. A., & Ng, J. D. (2014). Blepharophimosis syndrome with absent tear production. *Ophthalmic Plastic and Reconstructive Surgery*,

The purpose of this report was to present a case of congenital alacrima in a patient with blepharophimosis-ptosis-epicanthus inversus syndrome (BPES). A 9-month-old boy presented with characteristic clinical findings of BPES confirmed by genetic testing. On further history taking and evaluation, the patient was noted to have no tear production, despite clinically present palpebral lobes of the lacrimal glands. BPES is an autosomal dominant condition characterized by narrowed horizontal palpebral fissures, severe bilateral symmetric ptosis, epicanthus inversus, and telecanthus. To the authors' knowledge, this represents the second reported case of congenital alacrima in this syndrome. The first case described in the literature was in a 9-month-old girl who had congenital absence of the lacrimal glands. BPES may present with alacrima requiring vigilant lifelong lubrication and careful consideration in decisions for eyelid surgery including ptosis repair.

Nilsen, A., Miley, G. P., Forquer, I. P., Mather, M. W., Katneni, K., Li, Y., et al. (2014). Discovery, synthesis, and optimization of antimalarial 4(1 H)-quinolone-3-diarylethers. *Journal of Medicinal Chemistry*, 57(9), 3818-3834.

The historical antimalarial compound endochin served as a structural lead for optimization. Endochin-like quinolones (ELQ) were prepared by a novel chemical route and assessed for in vitro activity against multidrug resistant strains of *Plasmodium falciparum* and against malaria infections in mice. Here we describe the pathway to discovery of a potent class of orally active antimalarial 4(1H)-quinolone-3-diarylethers. The initial prototype, ELQ-233, exhibited low nanomolar IC50 values against all tested strains including clinical isolates harboring resistance to atovaquone. ELQ-271 represented the next critical step in the iterative optimization process, as it was stable to metabolism and highly effective in vivo. Continued analoging revealed that the substitution pattern on the benzenoid ring of the quinolone core significantly influenced reactivity with the host enzyme. This finding led to the rational design of highly selective ELQs with outstanding oral efficacy against murine malaria that is superior to established antimalarials chloroquine and atovaquone. © 2014 American Chemical Society.

Noone, J., Allen, T. L., Sullivan, M., McKenzie, G., Esqueda, T., & Ibarra, N. (2014). Escuchando a nuestros juvenes: A latino youth photovoice project on teen pregnancy. *Hispanic Health Care International : The Official Journal of the National Association of Hispanic Nurses*, 12(2), 63-70.

Half of Latina teens in the United States will become pregnant at least once by age 20 years. The purpose of this study was to explore a Pacific Northwest community's strengths and weaknesses, through photovoice, as viewed by Latino youth to understand their concerns related to teen pregnancy. Participants were asked to take photographs of what they believe contributes to preventing or increasing the risk of teen pregnancy. There were 14 Latino youth, ages 15-20 years, who enrolled in the study, and 9 completed all aspects of the project including public dissemination. The themes were categorized as (a) risks for teens, (b) pressure, (c) education is key, (d) community resources, and (e) Latino values. Presentations to the community generated dialogue and problem solving and laid the groundwork for planning interventions.

Novak, M. A., Hamel, A. F., Coleman, K., Lutz, C. K., Worlein, J., Menard, M., et al. (2014). Hair loss and hypothalamic-pituitary-adrenocortical axis activity in captive rhesus macaques (*macaca mulatta*). *Journal of the American Association for Laboratory Animal Science : JAALAS*, 53(3), 261-266.

Hair loss is a common problem in captive macaque colonies. A potential factor is the possible influence of stressful environments in the development of hair loss. We examined the relationship between hair loss and chronic hypothalamic-pituitary-adrenal (HPA) axis activity by measuring cortisol in hair. Adult male and female rhesus macaques housed at 3 primate facilities in the United States were screened for degree of hair loss and observed for evidence of hair-plucking behavior. Hair samples and photographic data were obtained from 99 subjects, none of which were hair-pluckers. Macaques with greater than 30% hair loss (alopecia group) showed higher concentrations of hair cortisol than did those with less than 5% hair loss (control group), a finding that was unrelated to age, body weight, or the month in which the sample was collected. Hair loss scores were positively correlated with hair cortisol levels across all monkeys and within the alopecic group alone. In addition, the strong relationship between hair cortisol and alopecia was noted in 2 but not the third facility. Friction with cage surfaces appeared to contribute to hair loss in 18 monkeys. These findings suggest that stress may be one of several factors related to

hair loss in some captive nonhuman primates, although whether this relationship is causal or merely correlational is unclear. Moreover, the source of the additional cortisol in the hair of alopecic monkeys (that is, from the circulation or from local synthesis in the skin) remains to be determined.

Novosad, S. A., & Winthrop, K. L. (2014). Beyond tumor necrosis factor inhibition: The expanding pipeline of biologic therapies for inflammatory diseases and their associated infectious sequelae. *Clinical Infectious Diseases*, *58*(11), 1587-1598.

Patients with rheumatoid arthritis and other immune-mediated inflammatory diseases are at higher risk for infectious morbidity and mortality, partially due to the therapies used to treat these conditions. Both prednisone and targeted biologic therapies such as tumor necrosis factor antagonists have been implicated to various degrees, although in some cases firm data are lacking with regard to certain types of infections. To date, there is a paucity of information regarding the infectious risks associated with the newer biologic agents. As new biologic agents become available for use, their potential infectious risks will challenge infectious disease clinicians who must work to prevent, diagnose, and treat infections in this setting. This article reviews our current understanding of infectious risk in the setting of targeted therapies and provides an update of the immune system targets and potential infectious sequelae of both current and emerging biologic therapies. © The Author 2014.

O'Glasser, A. Y., & Sauerwein, R. R. (2014). Recurrent melanoma presenting as a very large cardiac mass with concurrent pancreatic involvement. *Journal of General Internal Medicine*,

Oken, B., Ahani, A., Wahbeh, H., Nezamfar, H., Miller, M., Erdogmus, D., et al. (2014). Signal processing and machine learning of EEG and respiration changes during mindfulness meditation state. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *20*(5), A25.

Oken, B., Miller, M., Goodrich, E., & Wahbeh, H. (2014). Effects of mindfulness meditation on self-rated stress-related measures: Improvements in neuroticism and ecological momentary assessment of stress. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, *20*(5), A64.

Oken, B., Yu, J., Neuendorf, R., Wahbeh, H., & Hutchison, K. (2014). Systematic review of mind-body interventions on sleep. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A65.

Oken, B. S., Orhan, U., Roark, B., Erdogmus, D., Fowler, A., Mooney, A., et al. (2014). Brain-computer interface with language model-electroencephalography fusion for locked-in syndrome. *Neurorehabilitation and Neural Repair*, 28(4), 387-394.

Background. Some noninvasive brain-computer interface (BCI) systems are currently available for locked-in syndrome (LIS) but none have incorporated a statistical language model during text generation. Objective. To begin to address the communication needs of individuals with LIS using a noninvasive BCI that involves rapid serial visual presentation (RSVP) of symbols and a unique classifier with electroencephalography (EEG) and language model fusion. Methods. The RSVP Keyboard was developed with several unique features. Individual letters are presented at 2.5 per second. Computer classification of letters as targets or nontargets based on EEG is performed using machine learning that incorporates a language model for letter prediction via Bayesian fusion enabling targets to be presented only 1 to 4 times. Nine participants with LIS and 9 healthy controls were enrolled. After screening, subjects first calibrated the system, and then completed a series of balanced word generation mastery tasks that were designed with 5 incremental levels of difficulty, which increased by selecting phrases for which the utility of the language model decreased naturally. Results. Six participants with LIS and 9 controls completed the experiment. All LIS participants successfully mastered spelling at level 1 and one subject achieved level 5. Six of 9 control participants achieved level 5. Conclusions. Individuals who have incomplete LIS may benefit from an EEG-based BCI system, which relies on EEG classification and a statistical language model. Steps to further improve the system are discussed. © The Author(s) 2013.

Ostrogorsky, T. L., & Raber, A. M. (2014). Experience of first-year nursing students during an education redesign: Findings from the Oregon consortium for nursing education. *Nursing Education Perspectives*, 35(2), 115-121.

AIM The aim of this article is to summarize first-year students' (n = 908) experience during a

nursing education redesign. BACKGROUND Oregon Consortium for Nursing Education (OCNE) began its redesign of nursing education in 2000, long before the current national calls for nursing education reform. As OCNE moved from planning to implementation, a comprehensive evaluation of the students, the program, and curriculum ensued. METHOD Data were collected from first-year nursing students each spring from 2007-2010 using a standardized survey instrument that included demographic, attitudinal, and opinion-based survey items. RESULTS Results indicated fellow students, course lectures and interaction, and faculty and courses were rated areas of satisfaction. CONCLUSION Areas needing improvement included advising and facilities, administration, quality of instruction and curriculum, and overall program effectiveness. Mean scaled and open-ended responses from each area are reported.

Pal, P., Fox, J. M., Hawman, D. W., Huang, Y. J., Messaoudi, I., Kreklywich, C., et al. (2014).

Chikungunya viruses that escape monoclonal antibody therapy are clinically attenuated, stable, and not purified in mosquitoes. *Journal of Virology*,

Chikungunya virus (CHIKV) is a re-emerging mosquito-transmitted alphavirus that causes epidemics of debilitating polyarthritis in humans. A prior study identified two anti-CHIKV MAbs (CHK-152 and CHK-166) against the E2 and E1 structural proteins, which had therapeutic efficacy in immunocompetent and immunocompromised mice. Combination MAb therapy was required as administration of a single MAb resulted in the rapid selection of neutralization escape variants and treatment failure in mice. Here, we initially evaluated the efficacy of combination MAb therapy in a non-human primate model of CHIKV infection. Treatment of rhesus macaques with CHK-152 and CHK-166 reduced viral spread and infection in distant tissue sites and also neutralized reservoirs of infectious virus. Escape viruses were not detected in the residual viral RNA present in tissues and organs of rhesus macaques. To evaluate the possible significance of MAb resistance, we engineered neutralization escape variant viruses (E1-K61T, E2-D59N, and E1-K61T + E2-D59N) that conferred resistance to CHK-152 and CHK-166 and tested them for fitness in mosquito cells, mammalian cells, mice, and *Aedes albopictus* mosquitoes. In both cell culture and mosquitoes, the mutant viruses grew equivalently and did not revert to wild-type (WT) sequence. In mice, all escape variants showed evidence of mild clinical attenuation, with decreased musculoskeletal disease at early times after infection and a prolonged survival time in

immunocompromised *Ifnar1*^{-/-} mice. Unexpectedly, this was not associated with decreased infectivity, and consensus sequencing from tissues revealed no evidence of reversion or compensatory mutations. Competition studies with CHIKV WT also revealed no fitness compromise of the double mutant (E1-K61T + E2-D59N) neutralization escape variant in WT mice. Collectively, our study suggests that neutralization escape viruses selected during combination CHK-152 + CHK-166 MAb therapy retain fitness, cause less severe clinical disease, and likely would not be purified during the enzootic cycle. IMPORTANCE: Chikungunya virus (CHIKV) causes explosive epidemics of acute and chronic arthritis in humans in Africa, the Indian subcontinent, and Southeast Asia and recently has spread to the New World. As there are no approved vaccines or therapies for human use, the possibility of CHIKV-induced debilitating disease is high in many parts of the world. To this end, our laboratory recently generated a combination monoclonal antibody therapy that aborted lethal and arthritogenic disease in wild type and immunocompromised mice when administered as a single dose several days after infection. In this study, we show efficacy of the antibody combination in non-human primates and also evaluate the significance of possible neutralization escape mutations in mosquito and mammalian cells, mice, and *Aedes albopictus* vector mosquitoes. Our experiments show that escape viruses from combination antibody therapy cause less severe CHIKV clinical disease, retain fitness, and likely would not be purified by mosquito vectors.

Parker, D. L., Lee, S. W., Geszvain, K., Davis, R. E., Gruffaz, C., Meyer, J. M., et al. (2014).

Pyoverdine synthesis by the Mn(II)-oxidizing bacterium *Pseudomonas putida* GB-1. *Frontiers in Microbiology*, 5, 202.

When iron-starved, the Mn(II)-oxidizing bacteria *Pseudomonas putida* strains GB-1 and MnB1 produce pyoverdines (PVDGB-1 and PVDMnB1), siderophores that both influence iron uptake and inhibit manganese(II) oxidation by these strains. To explore the properties and genetics of a PVD that can affect manganese oxidation, LC-MS/MS, and various siderotyping techniques were used to identify the peptides of PVDGB-1 and PVDMnB1 as being (for both PVDs): chromophore-Asp-Lys-OHAsp-Ser-Gly-aThr-Lys-cOHO_{rn}, resembling a structure previously reported for *P. putida* CFML 90-51, which does not oxidize Mn. All three strains also produced an azotobactin and a sulfonated PVD, each with the peptide sequence above, but with unknown regulatory or

metabolic effects. Bioinformatic analysis of the sequenced genome of *P. putida* GB-1 suggested that a particular non-ribosomal peptide synthetase (NRPS), coded by the operon PputGB1_4083-4086, could produce the peptide backbone of PVDGB-1. To verify this prediction, plasmid integration disruption of PputGB1_4083 was performed and the resulting mutant failed to produce detectable PVD. In silico analysis of the modules in PputGB1_4083-4086 predicted a peptide sequence of Asp-Lys-Asp-Ser-Ala-Thr-Lys-Orn, which closely matches the peptide determined by MS/MS. To extend these studies to other organisms, various Mn(II)-oxidizing and non-oxidizing isolates of *P. putida*, *P. fluorescens*, *P. marincola*, *P. fluorescens-syringae* group, *P. mendocina-resinovorans* group, and *P. stutzerii* group were screened for PVD synthesis. The PVD producers (12 out of 16 tested strains) were siderotyped and placed into four sets of differing PVD structures, some corresponding to previously characterized PVDs and some to novel PVDs. These results combined with previous studies suggested that the presence of OHAsp or the flexibility of the pyoverdine polypeptide may enable efficient binding of Mn(III).

Peek, C. J., Cohen, D. J., & Degruy, F. V. (2014). Research and evaluation in the transformation of primary care. *The American Psychologist*, 69(4), 430-442.

Across the United States, primary care practices are engaged in demonstration projects and quality improvement efforts aimed at integrating behavioral health and primary care. Efforts to make sustainable changes at the frontline of care have identified new research and evaluation needs. These efforts enable clinics and larger health care communities to learn from demonstration projects regarding what works and what does not when integrating mental health, substance use, and primary care under realistic circumstances. To do this, implementers need to measure their successes and failures to inform local improvement processes, including the efforts of those working on integration in separate but similar settings. We review how new research approaches, beyond the contributions of traditional controlled trials, are needed to inform integrated behavioral health. Illustrating with research examples from the field, we describe how research traditions can be extended to meet these new research and learning needs of frontline implementers. We further suggest that a shared language and set of definitions for the field (not just for a particular study) are critical for the aggregation of knowledge and learning across

practices and for policymaking and business modeling. (PsycINFO Database Record (c) 2014 APA, all rights reserved).

Peluffo, M. C., Stanley, J., Braeuer, N., Rotgeri, A., Fritzscheier, K. H., Fuhrmann, U., et al. (2014). A prostaglandin E2 receptor antagonist prevents pregnancies during a preclinical contraceptive trial with female macaques. *Human Reproduction (Oxford, England)*,

STUDY QUESTION: Can administration of a prostaglandin (PG) E2 receptor 2 (PTGER2) antagonist prevent pregnancy in adult female monkeys by blocking periovulatory events in the follicle without altering menstrual cyclicity or general health? SUMMARY ANSWER: This is the first study to demonstrate that a PTGER2 antagonist can serve as an effective non-hormonal contraceptive in primates. WHAT IS KNOWN ALREADY: The requirement for PGE2 in ovulation and the release of an oocyte surrounded by expanded cumulus cells (cumulus-oocyte expansion; C-OE) was established through the generation of PTGS2 and PTGER2 null-mutant mice. A critical role for PGE2 in primate ovulation is supported by evidence that intrafollicular injection of indomethacin in rhesus monkeys suppressed follicle rupture, whereas co-injection of PGE2 with indomethacin resulted in ovulation. STUDY DESIGN, SIZE, DURATION: First, controlled ovulation protocols were performed in adult, female rhesus monkeys to analyze the mRNA levels for genes encoding PGE2 synthesis and signaling components in the naturally selected pre-ovulatory follicle at different times after the ovulatory hCG stimulus (0, 12, 24, 36 h pre-ovulation; 36 h post-ovulation, n = 3-4/time point). Second, controlled ovarian stimulation cycles were utilized to obtain multiple cumulus-oocyte complexes (COCs) from rhesus monkeys to evaluate the role of PGE2 in C-OE in vitro (n = 3-4 animals/treatment; ≥ 3 COCs/animal/treatment). Third, adult cycling female cynomolgus macaques were randomly assigned (n = 10/group) to vehicle (control) or PTGER2 antagonist (BAY06) groups to perform a contraceptive trial. After the first treatment cycle, a male of proven fertility was introduced into each group and they remained housed together for the duration of the 5-month contraceptive trial that was followed by a post-treatment reversibility trial. PARTICIPANTS/MATERIALS, SETTING, METHODS: Quantitative real-time PCR, COC culture and expansion, immunofluorescence/confocal microscopy, enzyme immunoassay, contraceptive trial, ultrasonography, complete blood counts, serum biochemistry tests and blood lipid profiles. MAIN RESULTS AND THE ROLE OF CHANCE: Several mRNAs

encoding proteins involved in PGE2 synthesis, metabolism and signaling increase ($P < 0.05$) in the periovulatory follicle after administration of an ovulatory hCG bolus. PGE2 signaling through PTGER2 induces cumulus cell expansion and production of hyaluronic acid, which are critical events for fertilization. Moreover, chronic administration of a selective PTGER2 antagonist resulted in a significant ($P < 0.05$ versus vehicle-treated controls) contraceptive effect without altering steroid hormone patterns or menstrual cyclicity during a 5-months contraceptive trial. Fertility recovered as early as 1 month after ending treatment. LIMITATIONS, REASONS FOR CAUTION: This is a proof-of-concept study in a non-human primate model. Further investigations are warranted to elucidate the mechanism(s) of PTGER2 antagonist action in the primate ovary. Although PTGER2 antagonist treatment did not produce any obvious undesirable effects, improvements in the mode of administration, as well as the efficacy of these compounds, are necessary to consider such a contraceptive for women. WIDER IMPLICATIONS OF THE FINDINGS: Monitoring as well as improving the efficacy and safety of female contraceptives is an important public health activity. Even though hormonal contraceptives are effective for women, concerns remain regarding their side-effects and long-term use because of the widespread actions of such steroidal products in many tissues. Moreover, some women cannot take hormones for medical reasons. Thus, development of non-hormonal contraceptives for women is warranted. STUDY FUNDING/COMPETING INTEREST(S): Supported by Bayer HealthCare Pharmaceuticals, The Eunice Kennedy Shriver NICHD Contraceptive Development and Research Center (U54 HD055744), NIH Office of the Director (Oregon National Primate Research Center P51 OD011092), and a Lalor Foundation Postdoctoral Basic Research Fellowship (MCP). The use of the Leica confocal was supported by grant number S10RR024585. Some of the authors (N.B., A.R., K.-H.F., U.F., B.B. and B.L.) are employees of Bayer Healthcare Pharma.

Pfeifer, C. S., Shelton, Z. R., Szczpanski, C. R., Barros, M. D., Wilson, N. D., & Stansbury, J. W. (2014). Tailoring heterogeneous polymer networks through polymerization-induced phase separation: Influence of composition and processing conditions on reaction kinetics and optical properties. *Journal of Polymer Science, Part A: Polymer Chemistry*, Polymerization-induced phase separation from an all-monomeric system by direct copolymerization offers the formation of heterogeneous polymeric structures without reliance on

polymer blends, block copolymers, or interpenetrating polymer networks. This study examines the potential for the formation of compositional heterogeneity in copolymer networks obtained by free-radical photopolymerizations of initially homogeneous mixtures of bisphenol A glycidyl dimethacrylate and isodecyl methacrylate as the comonomer ratios and polymerization conditions are varied. Comonomer proportions that control thermodynamic stability prior to (as determined by cloud point measurements) and during [as determined by turbidity measurements coupled with near-infrared (IR) spectroscopy] polymerization were shown to be a more influential factor on phase separation than irradiance-imposed kinetic control of the photopolymerization process. Through photorheometry coupled with near-IR and ultraviolet-visible (UV-Vis), the onset of phase separation was shown to occur at very low conversions and always prior to gelation (as estimated by the crossover of G'/G''). © 2014 Wiley Periodicals, Inc.

Pound, L. D., Comstock, S. M., & Grove, K. L. (2014). Consumption of a western-style diet during pregnancy impairs offspring islet vascularization in a Japanese macaque model. *American Journal of Physiology. Endocrinology and Metabolism*,

Children exposed to a maternal Western-style diet in utero have an increased risk of developing type 2 diabetes. Understanding the mechanisms and an investigation of possible interventions are critical to reversing this phenomenon. We examined the impact of maternal Western-style diet consumption on the development of islet vascularization and innervation, both critical to normal islet function, in fetal and juvenile offspring. Furthermore, we assessed whether improved dietary intake or resveratrol supplementation could ameliorate the harmful consequences of Western-style diet consumption during pregnancy. Adult female Japanese Macaques were maintained on a control or Western-style diet for 4-7 years. One cohort of dams was switched back onto a control diet while another cohort received resveratrol supplementation throughout gestation. Pregnancies were terminated in the early third trimester by C-section or offspring were born naturally and sent to necropsy at 1 year of age. Western-style diet consumption resulted in impaired fetal islet capillary density and sympathetic islet innervation. Furthermore, this reduction in vascularization persisted in the juvenile offspring. This effect is independent of changes in the expression of key angiogenic markers. Diet reversal normalized islet vascularization to control offspring levels while resveratrol supplementation caused a significant

increase in capillary density above controls. These data provide a novel mechanism by which maternal Western-style diet consumption leads to increased susceptibility to type 2 diabetes in the offspring. Importantly, an improved maternal diet may mitigate these harmful effects. However, until the long-term consequences of increased vascularization can be determined, resveratrol use during pregnancy is not advised.

Press, R. D. (2014). Clinical implementation of next-generation sequencing. *Clinical Advances in Hematology and Oncology*, 12(4), 263-265.

Punnen, S., Freedland, S. J., Presti Jr., J. C., Aronson, W. J., Terris, M. K., Kane, C. J., et al. (2014).

Multi-institutional validation of the CAPRA-S score to predict disease recurrence and mortality after radical prostatectomy. *European Urology*, 65(6), 1171-1177.

Background The University of California, San Francisco, Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score uses pathologic data from radical prostatectomy (RP) to predict prostate cancer recurrence and mortality. However, this clinical tool has never been validated externally. **Objective** To validate CAPRA-S in a large, multi-institutional, external database.

Design, setting, and participants The Shared Equal Access Regional Cancer Hospital (SEARCH) database consists of 2892 men who underwent RP from 2001 to 2011. With a median follow-up of 58 mo, 2670 men (92%) had complete data to calculate a CAPRA-S score. **Intervention** RP.

Outcome measurements and statistical analysis The main outcome was biochemical recurrence.

Performance of CAPRA-S in detecting recurrence was assessed and compared with a validated postoperative nomogram by concordance index (c-index), calibration plots, and decision curve analysis. Prediction of cancer-specific mortality was assessed by Kaplan-Meier analysis and the c-index.

Results and limitations The mean age was 62 yr (standard deviation: 6.3), and 34.3% of men had recurrence. The 5-yr progression-free probability for those patients with a CAPRA-S score of 0-2, 3-5, and 6-10 (defining low, intermediate, and high risk) was 72%, 39%, and 17%, respectively. The CAPRA-S c-index was 0.73 in this validation set, compared with a c-index of 0.72 for the Stephenson nomogram. Although CAPRA-S was optimistic in predicting the likelihood of being free of recurrence at 5 yr, it outperformed the Stephenson nomogram on both calibration plots and decision curve analysis. The c-index for predicting cancer-specific mortality

was 0.85, with the caveat that this number is based on only 61 events. Conclusions In this external validation, the CAPRA-S score predicted recurrence and mortality after RP with a c-index >0.70. The score is an effective prognostic tool that may aid in determining the need for adjuvant therapy. © 2013 European Association of Urology.

Purdom, E., Ho, C., Grasso, C. S., Quist, M. J., Cho, R. J., & Spellman, P. (2013). Methods and challenges in timing chromosomal abnormalities within cancer samples. *Bioinformatics (Oxford, England)*, 29(24), 3113-3120.

MOTIVATION: Tumors acquire many chromosomal amplifications, and those acquired early in the lifespan of the tumor may be not only important for tumor growth but also can be used for diagnostic purposes. Many methods infer the order of the accumulation of abnormalities based on their occurrence in a large cohort of patients. Recently, Durinck et al. (2011) and Greenman et al. (2012) developed methods to order a single tumor's chromosomal amplifications based on the patterns of mutations accumulated within those regions. This method offers an unprecedented opportunity to assess the etiology of a single tumor sample, but has not been widely evaluated.

RESULTS: We show that the model for timing chromosomal amplifications is limited in scope, particularly for regions with high levels of amplification. We also show that the estimation of the order of events can be sensitive for events that occur early in the progression of the tumor and that the partial maximum likelihood method of Greenman et al. (2012) can give biased estimates, particularly for moderate read coverage or normal contamination. We propose a maximum-likelihood estimation procedure that fully accounts for sequencing variability and show that it outperforms the partial maximum-likelihood estimation method. We also propose a Bayesian estimation procedure that stabilizes the estimates in certain settings. We implement these methods on a small number of ovarian tumors, and the results suggest possible differences in how the tumors acquired amplifications. AVAILABILITY AND IMPLEMENTATION: We provide implementation of these methods in an R package cancerTiming, which is available from the Comprehensive R Archive Network (CRAN) at <http://CRAN.R-project.org/>.

Puthussery, T., Percival, K. A., Venkataramani, S., Gayet-Primo, J., Grunert, U., & Taylor, W. R. (2014). Kainate receptors mediate synaptic input to transient and sustained OFF visual pathways

in primate retina. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 34(22), 7611-7621.

Visual signals are segregated into parallel pathways at the first synapse in the retina between cones and bipolar cells. Within the OFF pathways of mammals, the selective expression of AMPA or kainate-type glutamate receptors in the dendrites of different OFF-bipolar cell types is thought to contribute to formation of distinct temporal channels. AMPA receptors, with rapid recovery from desensitization, are proposed to transmit high temporal frequency signals, whereas kainate receptors (KARs) are presumed to encode lower temporal frequencies. Here we studied the glutamate receptors expressed by OFF-bipolar cells in slice preparations of macaque monkey retina, where the low (midget/parvocellular) and high-frequency (parasol/magnocellular) temporal channels are well characterized. We found that all OFF-bipolar types receive input primarily through KARs and that KAR antagonists block light-evoked input to both OFF-midget and OFF-parasol ganglion cells. KAR subunits were differentially expressed in OFF-bipolar types; the diffuse bipolar (DB) cells, DB2 and DB3b, expressed GluK1 and showed transient responses to glutamate and the KAR agonist, ATPA. In contrast, flat midget bipolar, DB1, and DB3a cells lacked GluK1 and showed relatively sustained responses. Finally, we found that the KAR accessory protein, Neto1, is expressed at the base of cone pedicles but is not colocalized with the GluK1 subunit. In summary, the results indicate that transient signaling in the OFF pathway of macaques is not dependent on AMPA receptors and that heterogeneity of KARs and accessory proteins may contribute to the formation of parallel temporal channels.

Raber, J., Rudbeck, E., Campbell-Beachler, M., Allen, A. R., Allen, B., Rosi, S., et al. (2014).

28Silicon radiation-induced enhancement of synaptic plasticity in the hippocampus of naïve and cognitively tested mice. *Radiation Research*, 181(4), 362-368.

The space radiation environment consists of multiple species of high-energy charge particles (HZE), including ⁵⁶Fe and ²⁸Si nuclei, that may impact neuronal cells, but their damaging effects on the central nervous system (CNS) have been poorly defined. Hippocampus-dependent memory functions have been shown to be highly sensitive to ⁵⁶Fe HZE particles, which poses a significant risk to the cognitive performance of astronauts during space missions. While low doses of ⁵⁶Fe radiation do not induce cell death of mature neurons, they affect synaptic plasticity in the

CA1 region, the principal neuronal output of the hippocampal formation involved in memory formation. The effects of ²⁸Si on the CNS have not been defined. Compared to behaviorally naïve mice, cognitive testing might affect synaptic plasticity and the effects of ²⁸Si radiation on synaptic plasticity might be modulated by prior cognitive testing. Therefore, in the current study, we quantified the effects of whole-body ²⁸Si radiation (600 MeV/n, 0.25 and 1 Gy) on hippocampus-dependent contextual freezing and synaptic plasticity in the CA1 region of animals not exposed (behaviorally naïve mice) and animals exposed to the contextual freezing test (cognitively tested mice). In behaviorally naïve mice exposed to 0.25 and 1 Gy of ²⁸Si radiation, the magnitude of long-term potentiation (LTP) was enhanced. However, in mice irradiated with 0.25 Gy contextual fear conditioning was enhanced and was associated with a further enhancement of the LTP magnitude. Such increase in synaptic plasticity was not seen in cognitively tested mice irradiated with 1 Gy. Thus, low dose ²⁸Si radiation has effects on synaptic plasticity in the CA1 region of the hippocampus and these effects are modulated by cognitive testing in a contextual fear-conditioning test. © 2014 by Radiation Research Society.

Rajhbeharrysingh, U., Taylor, M., & Milas, M. (2014). Medical therapy for advanced forms of thyroid cancer. *The Surgical Clinics of North America*, 94(3), 541-571.

More options than ever before are currently available for medical therapy in patients who present with advanced thyroid cancer or develop surgically unresectable recurrences or symptomatic or progressive disease. The newer medical therapies have addressed the need to find effective therapies beyond the conventional treatment with radioactive iodine, thyroid stimulating hormone suppression, and palliative cytotoxic chemotherapy for patients with advanced thyroid cancer. Although tumor responses to these medical therapies vary by type of thyroid cancer and type of therapy selected, they remain encouraging and provide therapeutic options for selected patients while new drugs are in development.

Ramaker, M. J., Ford, M. M., Phillips, T. J., & Finn, D. A. (2014). Differences in the reinstatement of ethanol seeking with ganaxolone and gaboxadol. *Neuroscience*, 272C, 180-187.

The endogenous neuroactive steroid allopregnanolone (ALLO) has previously been shown to induce reinstatement of ethanol seeking in rodents. ALLO is a positive allosteric modulator at

both synaptic and extrasynaptic GABAA receptors. The contribution of each class of GABAA receptors in mediating reinstatement of ethanol seeking is unknown. The first aim of the present study was to determine whether ganaxolone (GAN), a longer-acting synthetic analog of ALLO, also promotes reinstatement of ethanol seeking. The second aim was to examine whether preferentially activating extrasynaptic GABAA receptors with the selective agonist gaboxadol (THIP) was sufficient to reinstate responding for ethanol in mice. Male C57BL/6J mice were trained to lever press for access to a 10% ethanol (v/v) solution (10E), using a sucrose-fading procedure. Following extinction of the lever-pressing behavior, systemic THIP (0, 4 and 6mg/kg) and GAN (0, 10, and 15mg/kg) were tested for their ability to reinstate ethanol-appropriate responding in the absence of 10E access. GAN significantly increased lever pressing on the previously active lever, while THIP did not alter lever-pressing behavior. The results of this study suggest that direct activation of extrasynaptic GABAA receptors at the GABA site is not sufficient to induce ethanol seeking in the reinstatement procedure. Future studies are necessary to elucidate the mechanisms and brain areas by which differences in the pharmacological activity of GAN and THIP at the GABAA receptor contribute to the dissimilarity in their effect on the reinstatement of ethanol seeking. Nonetheless, based on the increased use of these drugs in clinical trials across multiple disease states, the effects of GAN or THIP on alcohol seeking may be an important consideration if these drugs are to be used clinically in a population with a co-occurring alcohol use disorder.

Reba, S. M., Li, Q., Onwuzulike, S., Ding, X., Karim, A. F., Hernandez, Y., et al. (2014). TLR2 engagement on CD4+ T cells enhances effector functions and protective responses to mycobacterium tuberculosis. *European Journal of Immunology*, 44(5), 1410-1421.

We have previously demonstrated that mycobacterial lipoproteins engage TLR2 on human CD4+ T cells and upregulate TCR-triggered IFN- γ secretion and cell proliferation in vitro. Here we examined the role of CD4+ T-cell-expressed TLR2 in Mycobacterium tuberculosis (MTB) Ag-specific T-cell priming and in protection against MTB infection in vivo. Like their human counterparts, mouse CD4+ T cells express TLR2 and respond to TLR2 costimulation in vitro. This Th1-like response was observed in the context of both polyclonal and Ag-specific TCR stimulation. To evaluate the role of T-cell TLR2 in priming of CD4+ T cells in vivo, naive MTB Ag85B-specific

TCR transgenic CD4⁺ T cells (P25 TCR-Tg) were adoptively transferred into Tlr2^{-/-} recipient C57BL/6 mice that were then immunized with Ag85B and with or without TLR2 ligand Pam3Cys-SKKKK. TLR2 engagement during priming resulted in increased numbers of IFN- γ -secreting P25 TCR-Tg T cells 1 week after immunization. P25 TCR-Tg T cells stimulated in vitro via TCR and TLR2 conferred more protection than T cells stimulated via TCR alone when adoptively transferred before MTB infection. Our findings indicate that TLR2 engagement on CD4⁺ T cells increases MTB Ag-specific responses and may contribute to protection against MTB infection. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Reinier, K., Marijon, E., Uy-Evanado, A., Teodorescu, C., Narayanan, K., Chugh, H., et al. (2014). The association between atrial fibrillation and Sudden cardiac death. The Relevance of heart failure. *JACC: Heart Failure*,

Objectives: The purpose of this study was to evaluate the role of congestive heart failure (CHF) in the association between atrial fibrillation (AF) and sudden cardiac death (SCD). Background: Recent studies have reported the possibility of an independent association between AF and SCD. We hypothesized that a history of CHF is a significant confounder of this association. Methods: In a prospective case-control analysis from the community (The Oregon-SUDS [Sudden Unexpected Death Study], 2002 to 2012), SCD cases (n = 652) with clinical records available (including electrocardiography and/or echocardiography) were compared with age- and sex-matched control patients with coronary artery disease. The association between AF and SCD was analyzed using multivariable logistic regression and propensity score matching. Results: Cases (age 67.3 \pm 11.7 years, 65% male) were more likely than control patients (age 67.2 \pm 11.4 years, 65% male) to have a history of AF (p = 0.0001), myocardial infarction (p = 0.007), CHF (p < 0.0001), stroke (p < 0.0001), and diabetes (p < 0.0001). In multivariate analysis without considering CHF, AF was a significant predictor of SCD (odds ratio [OR]: 1.6; 95% confidence interval [CI]: 1.2 to 2.0; p = 0.002). However, in a model that included CHF, the AF-SCD association was no longer significant (OR: 1.1; 95% CI: 0.8 to 1.5; p = 0.45), whereas CHF was a significant predictor of SCD (OR: 3.1; 95% CI: 2.4 to 4.1; p < 0.0001). Results on the basis of propensity score matching were consistent. Conclusions: Our findings suggest that a history of CHF, including both

systolic and diastolic symptomatic dysfunction, may partially explain the AF-SCD association. ©
2014 American College of Cardiology Foundation.

Repka, M. X., Kraker, R. T., Holmes, J. M., Summers, A. I., Glaser, S. R., Barnhardt, C. N., et al.

(2014). Atropine vs patching for treatment of moderate amblyopia: Follow-up at 15 years of age of a randomized clinical trial. *JAMA Ophthalmology*,

IMPORTANCE Initial treatment for amblyopia of the fellow eye with patching and atropine sulfate eyedrops improves visual acuity. Long-term data on the durability of treatment benefit are needed. OBJECTIVE To report visual acuity at 15 years of age among patients who were younger than 7 years when enrolled in a treatment trial for moderate amblyopia. DESIGN, SETTING, AND PARTICIPANTS In a multicenter clinical trial, 419 children with amblyopia (visual acuity, 20/40 to 20/100) were randomly assigned to patching (minimum of 6 h/d) or atropine sulfate eyedrops, 1% (1 drop daily), for 6 months. Treatment after 6 months was at the discretion of the investigator. Two years after enrollment, an unselected subgroup of 188 children were enrolled into long-term follow-up. INTERVENTION Initial treatment with patching or atropine with subsequent treatment at investigator discretion. MAIN OUTCOMES AND MEASURES Visual acuity at 15 years of age with the electronic Early Treatment Diabetic Retinopathy Study test in amblyopic and fellow eyes. RESULTS Mean visual acuity in the amblyopic eye measured in 147 participants at 15 years of age was 0.14 logMAR (approximately 20/25); 59.9% of amblyopic eyes had visual acuity of 20/25 or better and 33.3%, 20/20 or better. Mean interocular acuity difference (IOD) at 15 years of age was 0.21 logMAR (2.1 lines); 48.3% had an IOD of 2 or more lines and 71.4%, 1 or more lines. Treatment (other than spectacles) was prescribed for 9 participants (6.1%) aged 10 to 15 years. Mean IOD was similar at examinations at 10 and 15 years of age (2.0 and 2.1 logMAR lines, respectively; $P = .39$). Better visual acuity at the 15-year examination was achieved in those who were younger than 5 years at the time of entry into the randomized clinical trial (mean logMAR, 0.09) compared with those aged 5 to 6 years (mean logMAR, 0.18; $P < .001$). When we compared subgroups based on original treatment with atropine or patching, no significant differences were observed in visual acuity of amblyopic and fellow eyes at 15 years of age ($P = .44$ and $P = .43$, respectively). CONCLUSIONS AND RELEVANCE At 15 years of age, most children treated for moderate amblyopia when younger

than 7 years have good visual acuity, although mild residual amblyopia is common. The outcome is similar regardless of initial treatment with atropine or patching. The results indicate that improvement occurring with amblyopia treatment is maintained until at least 15 years of age.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00000170.

Rosen, D. E. (2014). The development of outpatient milestones. *Academic Psychiatry : The Journal of the American Association of Directors of Psychiatric Residency Training and the Association for Academic Psychiatry*,

Rosenbaum, J. T., Lin, P., Asquith, M., Costello, M. E., Kenna, T. J., & Brown, M. A. (2014). Does the microbiome play a causal role in spondyloarthritis? *Clinical Rheumatology*,

The purpose of this study is to review the potential causal role of the microbiome in the pathogenesis of spondyloarthritis. The method used for the study is literature review. The microbiome plays a major role in educating the immune response. The microbiome is strongly implicated in inflammatory bowel disease which has clinical and genetic overlap with spondyloarthritis. The microbiome also plays a causal role in bowel and joint disease in HLA B27/human beta 2 microglobulin transgenic rats. The mechanism(s) by which HLA B27 could influence the microbiome is unknown but theories include an immune response gene selectivity, an effect on dendritic cell function, or a mucosal immunodeficiency. Bacteria are strongly implicated in the pathogenesis of spondyloarthritis. Studies to understand how HLA B27 affects bacterial ecosystems should be encouraged.

Rosenstock, J., Fonseca, V., Schinzel, S., Dain, M. P., Mullins, P., & Riddle, M. (2014). Reduced risk of hypoglycemia with once-daily glargine versus twice-daily NPH and number needed to harm with NPH to demonstrate the risk of one additional hypoglycemic event in type 2 diabetes: Evidence from a long-term controlled trial. *Journal of Diabetes and its Complications*,

AIMS: This analysis evaluated HbA1c-adjusted hypoglycemia risk with glargine versus neutral protamine Hagedorn (NPH) over a 5-year study in patients with Type 2 diabetes mellitus (T2DM). Clinical significance was assessed using number needed to harm (NNH) to demonstrate the risk of one additional patient experiencing at least one hypoglycemic event. METHODS: Individual patient-level data for symptomatic documented hypoglycemia and HbA1c values from a 5-year

randomized study comparing once-daily glargine (n=513) with twice-daily NPH (n=504) were analyzed. Symptomatic hypoglycemia was categorized according to concurrent self-monitoring blood glucose levels and need for assistance. Hypoglycemic events per patient-year as a function of HbA1c were fitted by negative binomial regression using treatment and HbA1c at endpoint as independent variables. An estimate of NNH was derived from logistic regression models.

RESULTS: The cumulative number of symptomatic hypoglycemia events was consistently lower with glargine compared with NPH over 5 years. Compared with twice-daily NPH, once-daily glargine treatment resulted in significantly lower adjusted odds ratios (OR) for all daytime hypoglycemia (OR 0.74; p=0.030) and any severe event (OR 0.64; p=0.035), representing a 26% and 36% reduction in the odds of daytime and severe hypoglycemia, respectively. Our model predicts that, if 25 patients were treated with NPH instead of glargine, then one additional patient would experience at least one severe hypoglycemic event. **CONCLUSIONS:** This analysis of long-term insulin treatment confirms findings from short-term studies and demonstrates that glargine provides sustained, clinically meaningful reductions in risk of hypoglycemia compared with NPH in patients with T2DM.

Sabol, B. A., de Sam Lazaro, S., Salati, J., Allen, A., Snowden, J., & Caughey, A. B. (2014). Racial and ethnic differences in pregnancy outcomes in women with chronic hypertension. *Obstetrics and Gynecology*, 123 Suppl 1, 168S-9S.

INTRODUCTION: This study evaluates the association between race and ethnicity and obstetric outcomes in women with chronic hypertension. **METHODS:** A retrospective cohort study of African American, Hispanic, Asian, and white California residents who delivered live, singleton, nonanomalous neonates from 2005 to 2008. The data consisted of birth records linked to hospital discharge data; chronic hypertension was identified by International Classification of Diseases, 9th Revision codes. Univariate and multivariable analyses were conducted to examine the association between chronic hypertension and preeclampsia, gestational diabetes, preterm delivery, birth weight, intrauterine fetal demise, neonatal death, and postneonatal death.

RESULTS: After accounting for education level, socioeconomic status, maternal age, and parity, African American, Hispanic, and Asian women with chronic hypertension were significantly more likely than whites to develop preeclampsia and deliver preterm (P<.001). African American

women had a significantly elevated risk of intrauterine fetal demise ($P < .001$) and postneonatal death ($P < .05$). Hispanic and Asian women were significantly more likely to develop gestational diabetes ($P < .001$). There were no significant differences in neonatal death (). Mean birth weights were significantly less for each race and ethnicity: African American (2,891 g), Hispanic (3,053 g), and Asian (2,933 g) when compared with whites (3,221 g) ($P < .001$). (Table is included in full-text article.) CONCLUSION: : Racial and ethnic disparities affect maternal and neonatal outcomes in women whose pregnancies are complicated by chronic hypertension. Whether this represents disparities in quality of care compared with biologic differences requires further investigation.

Sangvanich, T., Morry, J., Fox, C., Ngamcherdtrakul, W., Goodyear, S., Castro, D., et al. (2014).

Novel oral detoxification of mercury, cadmium, and lead with thiol-modified nanoporous silica. *ACS Applied Materials and Interfaces*, 6(8), 5483-5493.

We have developed a thiol-modified nanoporous silica material (SH-SAMMS) as an oral therapy for the prevention and treatment of heavy metal poisoning. SH-SAMMS has been reported to be highly efficient at capturing heavy metals in biological fluids and water. Herein, SH-SAMMS was examined for efficacy and safety in both in vitro and in vivo animal models for the oral detoxification of heavy metals. In simulated gastrointestinal fluids, SH-SAMMS had a very high affinity (K_d) for methyl mercury (MeHg(I)), inorganic mercury (Hg(II)), lead (Pb(II)), and cadmium (Cd(II)) and was superior to other SAMMS with carboxylic acid or phosphonic acid ligands or commercially available metal chelating sorbents. SH-SAMMS also effectively removed Hg from biologically digested fish tissue with no effect on most nutritional minerals found in fish. SH-SAMMS could hold Hg(II) and MeHg(I) tightly inside the nanosize pores, thus preventing bacteria from converting them to more absorbable forms. Rats fed a diet containing MeHg(I), Cd(II), and Pb(II) and SH-SAMMS for 2 weeks had blood Hg levels significantly lower than rats fed the metal-rich diet only. Upon cessation of the metal-rich diet, continued administration of SH-SAMMS for 2 weeks facilitated faster and more extensive clearance of Hg than in animals not continued on oral SH-SAMMS. Rats receiving SH-SAMMS also suffered less weight loss as a result of the metal exposure. Retention of Hg and Cd in major organs was lowest in rats fed with SH-SAMMS throughout the entire four weeks. The reduction of blood Pb by SH-SAMMS was significant. SH-SAMMS was safe to intestinal epithelium model (Caco-2) and common intestinal

bacteria (*Escherichia coli*). Altogether, it has great potential as a new oral drug for the treatment of heavy metal poisoning. This new application is enabled by the installation of tailored interfacial chemistry upon nontoxic nanoporous materials. © 2014 American Chemical Society.

Schaefer, C., Mann, R., Sadosky, A., Daniel, S., Parsons, B., Nalamachu, S., et al. (2014). Health status, function, productivity, and costs among individuals with idiopathic painful peripheral neuropathy with small fiber involvement in the united states: Results from a retrospective chart review and cross-sectional survey. *Journal of Medical Economics*, 17(6), 394-407.

Objective: To characterize the burden of idiopathic painful peripheral neuropathy with small fiber involvement (idiopathic SFN) by pain severity in the US. Methods: One hundred previously diagnosed idiopathic SFN subjects were enrolled during routine office visits. Subjects completed a one-time questionnaire, and investigators reported clinical characteristics and healthcare resource use, based on 6 month retrospective chart review. Annualized direct and indirect costs were estimated. Results were stratified across pain severity groups. Results: Mean age was 63.5 years; 53.0% were female; 76.0% had moderate or severe pain. Most common comorbidities were sleep disturbance/insomnia (37.0%), anxiety (34.0%), and depressive symptoms (33.0%). Overall mean health status (0.59; -0.11-1.00 scale), physical and mental health (31.7 and 45.6, respectively, 0-100 scale), sleep index (45.1; 0-100 scale), and pain interference with function (5.0; 0-10 scale) differed by pain severity, with worse outcomes among those with greater pain (all $p < 0.002$). 84.0% were prescribed 1 SFN medication. 16.0% were employed; mean overall work impairment was 36.9%. Annualized average adjusted direct and indirect costs per subject (\$8055 and \$13,733, respectively) differed by pain severity. Conclusions: Idiopathic SFN subjects with pain experience moderate or severe pain, which negatively impacts health status, function, and productivity, and leads to substantial direct and indirect costs. © 2014 All rights reserved: reproduction in whole or part not permitted.

Schenning, R., Vajtai, P., Troxell, M., Pollock, J., & Hopkins, K. (2013). Alveolar soft part sarcoma: Unusual etiology of mediastinal mass in an adolescent. *Clinics and Practice*, 3(2), e26.

Alveolar soft part sarcoma (ASPS) is a rare malignancy that usually arises in an extremity. Mediastinal involvement is uncommon, with only two reports of primary mediastinal disease and

two reports of metastatic mediastinal disease in the literature, all referencing adult patients. To our knowledge, ours is the first report of ASPS presenting with a mediastinal mass in adolescence. Although ASPS is not generally included in the differential for adolescent mediastinal masses, it should be considered when clinical presentation and imaging appearance are characteristic.

Schlansky, B., Chen, Y., Scott, D. L., Austin, D., & Naugler, W. E. (2014). Waiting time predicts survival after liver transplantation for hepatocellular carcinoma: A cohort study in the unos registry. *Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*,

Background. Recipients of liver transplantation (LT) for hepatocellular carcinoma (HCC) harbor an 8-20% risk of HCC recurrence. Single-center studies suggest that a period of waiting after HCC therapy may facilitate selection of patients at low risk for post-LT HCC recurrence and mortality. We evaluated whether longer waiting time after MELD prioritization for HCC predicts longer post-LT survival. Methods. In the United Network for Organ Sharing registry, we selected 2 groups registered for LT from March 2005 to March 2009: (1) HCC receiving MELD prioritization, and (2) non-HCC. Patients were stratified by MELD status at LT, a marker of time on the wait list after HCC MELD prioritization, and followed from LT until death or censoring through October 2012. We assessed predictors of post-LT survival and estimated the benefit of LT by comparing post-LT survival to the intention-to-treat (ITT) survival from registration. Results. The median MELDs at LT were 22 (HCC) and 24 (non-HCC). Increasing MELD at LT was independently associated with lower post-LT mortality in the HCC group (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.73-0.98) and higher post-LT mortality in the non-HCC group (HR: 1.20; 95% CI: 1.15-1.25). Compared to the HCC group, the non-HCC group had lower post-LT mortality (relative risk [RR]: 0.85; log-rank $p < 0.01$) but higher ITT mortality (RR: 1.25; log-rank $p < 0.01$), due to a 33 percentage-point lower probability of receiving LT. Conclusion. Longer waiting time before LT for HCC predicted longer post-LT survival in a national transplant registry. Delaying LT for HCC may reduce disparities in ITT survival and access to LT among different indications, thereby improving system utility and organ allocation equity in the overall pool of LT candidates. *Liver Transpl*, 2014. (c) 2014 AASLD.

Schmitz, K., Snyder, K., Geldermann, D., & Sohaey, R. (2014). The large pediatric scrotum:

Ultrasound technique and differential considerations. *Ultrasound Quarterly*, 30(2), 119-134.

Scrotal enlargement in the pediatric population is caused by a variety of pathologic processes including hydroceles, hernias, varicoceles, testicular torsion, testicular or paratesticular infection, trauma, or neoplasm; adrenal rests; or scrotal skin edema. The clinical presentation of scrotal enlargement is often nonspecific, and ultrasound plays a key role in making the correct diagnosis. In this pictorial review, we review the ultrasound protocol for performing scrotal ultrasound in pediatric patients and illustrate the ultrasound appearance of conditions resulting in scrotal enlargement.

Schnell, E., Long, T. H., Bensen, A. L., Washburn, E. K., & Westbrook, G. L. (2014). Neuroligin-1 knockdown reduces survival of adult-generated newborn hippocampal neurons. *Frontiers in Neuroscience*, 8, 71.

Survival of adult-born hippocampal granule cells is modulated by neural activity, and thought to be enhanced by excitatory synaptic signaling. Here, we report that a reduction in the synaptogenic protein neuroligin-1 in adult-born neurons in vivo decreased their survival, but surprisingly, this effect was independent of changes in excitatory synaptic function. Instead, the decreased survival was associated with unexpected changes in dendrite and spine morphology during granule cell maturation, suggesting a link between cell growth and survival.

Schulman, P. M., Merkel, M. J., & Rozner, M. A. (2013). Accidental, unintentional reprogramming of a temporary external pacemaker leading to R-on-T and cardiac arrest. *Journal of Cardiothoracic and Vascular Anesthesia*, 27(5), 944-948.

Schulman, P. M., & Rozner, M. A. (2014). In response. *Anesthesia and Analgesia*, 118(5), 1140-1141.

Senders, A., Hanes, D., Bourdette, D., Whitham, R., & Shinto, L. (2014). Improving the patient-reported outcome experience for participants and PI's: Feasibility and validity of PROMIS. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A13.

Senders, A., Yadav, V., & Shinto, L. (2014). The relationship between mindfulness and pain in multiple sclerosis. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A67.

Shaaban, A. M., Rezvani, M., Elsayes, K. M., Baskin, H., Jr, Mourad, A., Foster, B. R., et al. (2014). Ovarian malignant germ cell tumors: Cellular classification and clinical and imaging features. *Radiographics : A Review Publication of the Radiological Society of North America, Inc*, 34(3), 777-801.

Ovarian malignant germ cell tumors (OMGCTs) are heterogeneous tumors that are derived from the primitive germ cells of the embryonic gonad. OMGCTs are rare, accounting for about 2.6% of all ovarian malignancies, and typically manifest in adolescence, usually with abdominal pain, a palpable mass, and elevated serum tumor marker levels, which may serve as an adjunct in the initial diagnosis, monitoring during therapy, and posttreatment surveillance. Dysgerminoma, the most common malignant germ cell tumor, usually manifests as a solid mass. Immature teratomas manifest as a solid mass with scattered foci of fat and calcifications. Yolk sac tumors usually manifest as a mixed solid and cystic mass. Capsular rupture or the bright dot sign, a result of increased vascularity and the formation of small vascular aneurysms, may be present. Embryonal carcinomas and polyembryomas rarely manifest in a pure form and are more commonly part of a mixed germ cell tumor. Some OMGCTs have characteristic features that allow a diagnosis to be confidently made, whereas others have nonspecific features, which make them difficult to diagnose. However, imaging features, the patient's age at presentation, and tumor markers may help establish a reasonable differential diagnosis. Malignant ovarian germ cell tumors spread in the same manner as epithelial ovarian neoplasms but are more likely to involve regional lymph nodes. Preoperative imaging may depict local extension, peritoneal disease, and distant metastases. Suspicious areas may be sampled during surgery. Because OMGCTs are almost always unilateral and are chemosensitive, fertility-sparing surgery is the standard of care. (c)RSNA, 2014.

Shannonhouse, J. L., Urbanski, H. F., Woo, S. L., Fong, L. A., Goddard, S. D., Lucas, W. F., et al. (2014). Aquaporin-11 control of testicular fertility markers in syrian hamsters. *Molecular and Cellular Endocrinology*, 391(1-2), 1-9.

The present study sought novel changes to the hamster testicular transcriptome during modulation of fertility by well-characterized photoperiodic stimuli. Transition from long days (LD, 14h light/day) to short days (SD, 10h light/day) triggered testicular regression (61% reduction of testis weight, relative to LD) in SD-sensitive (SD-S) hamsters within 16weeks. After 22weeks of SD exposure, a third cohort of hamsters became SD-refractory (SD-R), and exhibited testicular recrudescence (137% testis weight gain, relative to SD-S). Partial interrogation of the testicular transcriptome by annealing-control-primer-modified differential display PCR provided several candidates for regulation of testicular functions. Multiple linear regression modeling indicated the best correlation for aquaporin 11 (Aqp11) with changes in testis weight. Correlations were also strongest for Aqp11 with expression levels of reference cDNAs that control spermatogenesis (Hspa2 and Tnp2), steroidogenesis (Cox2, 3betaHsd, and Srebp2), sperm motility (Catsper1, Pgc2, and Tnp2), inflammation (Cox2), and apoptosis (Bax and Bcl2). Moreover, siRNA-mediated knockdown of testicular Aqp11 mRNA and protein reduced Hspa2 and Tnp2 mRNA levels, and it increased 3betaHsd mRNA levels. It also reduced mRNA levels for Sept12, which is a testis-specific inducer of spermatogenesis. These results suggest a central role for testicular Aqp11 signaling in the coordinate regulation of crucial components of fertility.

Sharff, K. A., Graber, C. J., Spindel, S. J., & Nguyen, H. M. (2014). Ceftriaxone for methicillin-sensitive staphylococcus aureus osteoarticular infections: A survey of infectious disease physicians' attitudes and review of the literature. *Infectious Diseases in Clinical Practice*, 22(3), 132-140.

The use of ceftriaxone for methicillin-sensitive *Staphylococcus aureus* (MSSA) osteoarticular infections in outpatient antimicrobial therapy remains controversial. Our informal survey of 135 academic and community infectious disease physicians suggests that only 96 (71.1%) are willing to use ceftriaxone for MSSA osteoarticular infections, 55 of which use it only infrequently (ie, 1%-19% of the time). Among the ceftriaxone users, most believe that there is a role for ceftriaxone in acute osteomyelitis (82.2%), chronic osteomyelitis (63.3%), osteomyelitis with uncomplicated bacteremia (61.1%), vertebral osteomyelitis (57.8%), and prosthetic infections (51.1%). We reviewed the clinical literature and analyzed ceftriaxone pharmacokinetics-pharmacodynamics to construct a clinical framework to optimally use ceftriaxone in osteoarticular infections. We

conclude that ceftriaxone may be a reasonable therapeutic option for acute, uncomplicated MSSA osteoarticular infections after adequate surgical debridement, particularly when ceftriaxone is given as 2 g daily for MSSA isolates with oxacillin minimal inhibitory concentration values of 0.5 µg/mL or less (corresponding to ceftriaxone minimal inhibitory concentration values of ≤4 µg/mL). Copyright © 2014 by Lippincott Williams & Wilkins.

Shenje, L. T., Andersen, P., Uosaki, H., Fernandez, L., Rainer, P. P., Cho, G. S., et al. (2014).

Precardiac deletion of numb and numblike reveals renewal of cardiac progenitors. *Elife*, 3, e02164.

Cardiac progenitor cells (CPCs) must control their number and fate to sustain the rapid heart growth during development, yet the intrinsic factors and environment governing these processes remain unclear. Here, we show that deletion of the ancient cell-fate regulator Numb (Nb) and its homologue Numblike (Nbl) depletes CPCs in second pharyngeal arches (PA2s) and is associated with an atrophic heart. With histological, flow cytometric and functional analyses, we find that CPCs remain undifferentiated and expansive in the PA2, but differentiate into cardiac cells as they exit the arch. Tracing of Nb- and Nbl-deficient CPCs by lineage-specific mosaicism reveals that the CPCs normally populate in the PA2, but lose their expansion potential in the PA2. These findings demonstrate that Nb and Nbl are intrinsic factors crucial for the renewal of CPCs in the PA2 and that the PA2 serves as a microenvironment for their expansion. DOI:

<http://dx.doi.org/10.7554/eLife.02164.001>.

Shi, X., Zhang, F., Urdang, Z., Dai, M., Neng, L., Zhang, J., et al. (2014). Thin and open vessel

windows for intra-vital fluorescence imaging of murine cochlear blood flow. *Hearing Research*, 313, 38-46.

Normal microvessel structure and function in the cochlea is essential for maintaining the ionic and metabolic homeostasis required for hearing function. Abnormal cochlear microcirculation has long been considered an etiologic factor in hearing disorders. A better understanding of cochlear blood flow (CoBF) will enable more effective amelioration of hearing disorders that result from aberrant blood flow. However, establishing the direct relationship between CoBF and other cellular events in the lateral wall and response to physio-pathological stress remains a challenge due to the lack

of feasible interrogation methods and difficulty in accessing the inner ear. Here we report on new methods for studying the CoBF in a mouse model using a thin or open vessel-window in combination with fluorescence intra-vital microscopy (IVM). An open vessel-window enables investigation of vascular cell biology and blood flow permeability, including pericyte (PC) contractility, bone marrow cell migration, and endothelial barrier leakage, in wild type and fluorescent protein-labeled transgenic mouse models with high spatial and temporal resolution. Alternatively, the thin vessel-window method minimizes disruption of the homeostatic balance in the lateral wall and enables study CoBF under relatively intact physiological conditions. A thin vessel-window method can also be used for time-based studies of physiological and pathological processes. Although the small size of the mouse cochlea makes surgery difficult, the methods are sufficiently developed for studying the structural and functional changes in CoBF under normal and pathological conditions. © 2014.

Shi, Y., & Martin, J. E. (2014). Tinnitus overview. *Seminars in Hearing, 35*(2), 65-73.

Tinnitus affects more than 10% of the population and can be a severe condition in ~0.5% of people. Although it is related to diseases of the auditory system in the majority of cases, involvement of nonauditory structures in the brain is an important pathophysiological mechanism in patients with severe tinnitus, who often also present with sleep difficulties, mood disturbances, and cognitive dysfunction. Comprehensive evaluation of a patient with tinnitus often requires application of evaluation tools beyond audiological tests. When managing patients with chronic tinnitus and no obvious treatable underlying conditions, employment of a combination of sound treatments, habituation therapies, psychological intervention, and pharmacological agents is often needed to minimize the impact of tinnitus on patients and to improve their functionality and quality of life. Future research on tinnitus, with appropriate designs and improved measurement tools, may help us better understand tinnitus and facilitate development of novel and effective treatments. © 2014 by Thieme Medical Publishers, Inc.

Shibata, S., Khemani, R. G., & Markovitz, B. (2014). Patient origin is associated with duration of endotracheal intubation and PICU length of stay for children with status asthmaticus. *Journal of Intensive Care Medicine, 29*(3), 154-159.

Objective: To describe intubation practices and duration of mechanical ventilation in children with status asthmaticus admitted from emergency departments (ERs) to pediatric intensive care units (PICUs). Design: Retrospective cohort study using the Virtual PICU Performance System database (VPS, LLC) of children with status asthmaticus admitted to a participating PICU between December 2003 and September 2006. The primary outcome measure was intubation prior to intensive care unit (ICU) admission. Secondary outcomes included length of intubation and medical length of stay. Setting: Thirty-five PICUs in the United States. Patients: Children who were intubated and mechanically ventilated during their ICU stay for asthma and were admitted from an ER. Results: A total of 4051 patients with status asthmaticus were identified. Intubation data were available from 35 of the 53 centers. Of all, 187 children were intubated for asthma, of which 157 were admitted from an ER and had complete data. Of all, 85 patients were from community hospital ERs and 72 were from the institution's own ER. In all, 115 (73%) patients were intubated prior to ICU admission and 42 (27%) patients were intubated after PICU admission. Of patients who received mechanical ventilation for status asthmaticus and were intubated prior to PICU admission, a greater proportion were intubated at community hospital ERs than in the institutions' own ERs. Eightyfive percent of the patients from community hospital ERs were intubated prior to PICU admission as opposed to 60% from institution's own ERs ($P = .0004$). However, median duration of intubation and PICU stay from community hospital ERs was significantly shorter than from the hospitals' own ERs (25 vs 42 hours $P = .011$; 57 vs 98 hours $P = .0013$, respectively). Logistic regression analysis revealed that after controlling for the effects of age, race, gender, and a revised version of the Paediatric Index of Mortality score of patients who were admitted for status asthmaticus and required mechanical ventilations, patients treated in community hospital ERs represented a greater proportion of preadmission intubation. The odds ratio for preadmission intubation was 5.1 if the patients arrived from community hospital ERs (95% confidence interval 1.91-13.6). Conclusion: Patients with status asthmaticus are more likely to be intubated when they are admitted from community hospital emergency rooms, although the duration of intubation and PICU stay is shorter. © The Author(s) 2012.

Shihab, F. S., Olyaei, A., Wiland, A., Mccague, K., & Norman, D. J. (2014). Tacrolimus exposure in the real world: An analysis from the mycophenolic acid observational REnal transplant study. *Clinical*

Transplantation,

Tacrolimus exposure and renal function data to 36 months post-transplant were analyzed from the prospective, observational Mycophenolic acid Observational REnal transplant (MORE) registry in which de novo kidney transplant patients were managed according to local practice. Tacrolimus trough (C₀) concentration at month 12 was stratified as low (<8 ng/mL) in 724 patients. Estimated glomerular filtration rate (eGFR) was stratified as low (<8 ng/mL) was observed in 47.7%, 34.1%, 26.8%, and 26.7% of patients at baseline and months 12, 24, and 36, respectively. Biopsy-proven acute rejection was similar to month 36 regardless of tacrolimus C₀ category at month 12. Tacrolimus C₀ >8 ng/mL vs. <8 ng/mL was observed in 47.7%, 34.1%, 26.8%, and 26.7% of patients at baseline and months 12, 24, and 36, respectively. Biopsy-proven acute rejection was similar to month 36 regardless of tacrolimus C₀ category at month 12. Tacrolimus C₀ >8 ng/mL vs. <8 ng/mL was observed in 47.7%, 34.1%, 26.8%, and 26.7% of patients at baseline and months 12, 24, and 36, respectively. Biopsy-proven acute rejection was similar to month 36 regardless of tacrolimus C₀ category at month 12. Tacrolimus C₀ >8 ng/mL vs. <8 ng/mL at month 12 was predictive of subsequent low eGFR compared to C₀ <6 ng/mL. © 2014 John Wiley & Sons A/S.

Shikany, J. M., Barrett-Connor, E., Ensrud, K. E., Cawthon, P. M., Lewis, C. E., Dam, T. - L., et al.

(2014). Macronutrients, diet quality, and frailty in older men. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences*, 69(6), 695-701.

Background. Frailty, a phenotype of multisystem impairment and expanding vulnerability, is associated with higher risk of adverse health outcomes not entirely explained by advancing age. We investigated associations of macronutrients, dietary fiber, and overall diet quality with frailty status in older community-dwelling men. Methods. Participants were 5,925 men aged ≥65 years enrolled in the Osteoporotic Fractures in Men (MrOS) study at six U.S. centers. Diet was assessed at baseline with a food frequency questionnaire. We assessed frailty status (robust, intermediate, or frail) at baseline and at a second clinic visit (a mean of 4.6 years later) using a slightly modified Cardiovascular Health Study frailty index. We used multinomial logistic regression to assess associations between macronutrient intake, dietary fiber, and the Diet Quality Index Revised with frailty status at baseline and at the second clinic visit. Results. At baseline, 2,748

(46.4%) participants were robust, 2,681 (45.2%) were intermediate, and 496 (8.4%) were frail. Carbohydrate, fat, protein, and dietary fiber showed no consistent associations with frailty status. Overall diet quality exhibited fairly consistent associations with frailty status. The Diet Quality Index Revised was inversely associated with frail status relative to robust status at the baseline visit (odds ratio for Q5 vs Q1 = 0.44, 95% confidence interval: 0.30, 0.63; p for trend < .0001) and at the second clinic visit (odds ratio for Q5 vs Q1 = 0.18, 95% confidence interval: 0.03, 0.97; p for trend = .0180). Conclusions. Overall diet quality was inversely associated with prevalent and future frailty status in this cohort of older men. © 2013 The Author.

Shinseki, M. S., Zusman, N. L., Hiratzka, J., Marshall, L. M., & Yoo, J. U. (2014). Association between advanced degenerative changes of the atlanto-dens joint and presence of dens fracture. *The Journal of Bone and Joint Surgery.American Volume*, 96(9), 712-717.

BACKGROUND: Dens fractures in elderly patients are often related to issues associated with aging. We examined the association between degenerative changes of the atlanto-dens joint and the risk of dens fracture. **METHODS:** We conducted a retrospective study of trauma patients, fifty-five years of age or older, who had undergone a computed tomography scan of the cervical spine as part of their admission to a single level-I trauma center. There were 1794 patients who met the inclusion criteria; scans were evaluated for all fifty-six who presented with a dens fracture and for a random sample of 736 without a dens fracture. Intraosseous cyst formation, synovitis, and joint space narrowing were recorded from the scans. The prevalence of degenerative changes was compared between patients with and patients without a dens fracture. **RESULTS:** An intraosseous cyst in the dens was found in 16.4% of the patients without a dens fracture and in 64.3% of those with a fracture ($p < 0.001$). The dens fracture extended through the existing cyst in twenty-four (66.7%) of thirty-six patients with a cyst and a dens fracture. Retro-dens synovitis was present in 4.2% of the patients without a dens fracture and 25.0% of those with a fracture ($p < 0.001$). After adjustment for age and sex, both cysts (odds ratio [OR] = 7.7, 95% confidence interval [CI] = 4.2 to 14.1) and synovitis (OR = 4.6, 95% CI = 2.1 to 10.0) were significantly associated with dens fracture. **CONCLUSIONS:** Intraosseous dens cysts and retro-dens synovitis were associated with dens fracture; those with a dens fracture were nearly eightfold more likely to have an intraosseous cyst and nearly fivefold more likely to have

synovitis compared with those without a dens fracture. Because the atlanto-dens joint is a synovial joint, its degeneration can lead to subchondral cyst formation and synovitis and predispose affected individuals to fracture. LEVEL OF EVIDENCE: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Sidbury, R., Davis, D. M., Cohen, D. E., Cordoro, K. M., Berger, T. G., Bergman, J. N., et al. (2014).

Guidelines of care for the management of atopic dermatitis: Section 3. management and treatment with phototherapy and systemic agents. *Journal of the American Academy of Dermatology*,

Atopic dermatitis is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2% to 3% of adults. This guideline addresses important clinical questions that arise in atopic dermatitis management and care, providing recommendations based on the available evidence.

In this third of 4 sections, treatment of atopic dermatitis with phototherapy and systemic immunomodulators, antimicrobials, and antihistamines is reviewed, including indications for use and the risk-benefit profile of each treatment option.

Siddiqui, F. A., Atkins, K. M., Diggs, B. S., Thomas, C. R., Jr, Hunter, J. G., & Dolan, J. P. (2014).

Overall survival analysis of neoadjuvant chemoradiotherapy and esophagectomy for esophageal cancer. *Journal of Gastrointestinal Oncology*, 5(2), 86-91.

BACKGROUND: Patients treated with neoadjuvant chemoradiotherapy (NAC) followed by esophagectomy are more likely to have negative margins at resection, be downstaged, and have improved overall survival (OS). The specific aim of this study was to analyze OS outcomes using NAC followed by esophagectomy at a single, tertiary care academic medical center. METHODS: We retrospectively analyzed 106 patients that underwent NAC with platinum-based chemotherapy plus 5-fluorouracil (5-FU) or capecitabine followed by esophagectomy from September 1996 to May 2011. OS was analyzed by the Kaplan Meier method. RESULTS: Initial staging determined that of 106 patients, 62% had stage III (n=66), 31% stage II (n=33), and 7% had stage I disease (n=7). Following NAC, 92.5% (n=98) were resected with negative (R0) margins and pathologic staging revealed 59% (n=62) were downstaged, 9% (n=10) were upstaged, and 32% (n=34) remained at the same stage. A pathologic complete response (pCR)

was achieved in 29% (n=31) of the cohort. Median OS was 35.2 months for all patients, 42 months for downstaged patients, 13 months when upstaged, and 17 months for those who remained at the same stage (P=0.08). OS by histological type was 30 months for adenocarcinoma and 71 months for squamous cell carcinoma (P=0.06). CONCLUSIONS: NAC was effective in downstaging 59% of patients and effectively increased the chance for an R0 resection. These patients, in turn, had improved OS compared to the median OS. Patients with squamous cell carcinoma showed a trend towards more favorable OS.

Šileikyte, J., Blachly-Dyson, E., Sewell, R., Carpi, A., Menabò, R., Di Lisa, F., et al. (2014). Regulation of the mitochondrial permeability transition pore by the outer membrane does not involve the peripheral benzodiazepine receptor (translocator protein of 18 kDa (TSPO)). *Journal of Biological Chemistry*, 289(20), 13769-13781.

Translocator protein of 18 kDa (TSPO) is a highly conserved, ubiquitous protein localized in the outer mitochondrial membrane, where it is thought to play a key role in the mitochondrial transport of cholesterol, a key step in the generation of steroid hormones. However, it was first characterized as the peripheral benzodiazepine receptor because it appears to be responsible for high affinity binding of a number of benzodiazepines to non-neuronal tissues. Ensuing studies have employed natural and synthetic ligands to assess the role of TSPO function in a number of natural and pathological circumstances. Largely through the use of these compounds and biochemical associations, TSPO has been proposed to play a role in the mitochondrial permeability transition pore (PTP), which has been associated with cell death in many human pathological conditions. Here, we critically assess the role of TSPO in the function of the PTP through the generation of mice in which the *Tspo* gene has been conditionally eliminated. Our results show that 1) TSPO plays no role in the regulation or structure of the PTP, 2) endogenous and synthetic ligands of TSPO do not regulate PTP activity through TSPO, 3) outer mitochondrial membrane regulation of PTP activity occurs through a mechanism that does not require TSPO, and 4) hearts lacking TSPO are as sensitive to ischemia-reperfusion injury as hearts from control mice. These results call into question a wide variety of studies implicating TSPO in a number of pathological processes through its actions on the PTP. © 2014 by The American Society for Biochemistry and Molecular Biology, Inc.

Silverberg, J. I., & Simpson, E. L. (2014). Associations of childhood eczema severity: A US population-based study. *Dermatitis : Contact, Atopic, Occupational, Drug*, 25(3), 107-114.

BACKGROUND: Little is known about the predictors of eczema severity in the US population.

OBJECTIVES: We sought to determine the distribution and associations of childhood eczema

severity in the United States. METHODS: We analyzed the data from the 2007 National Survey of Children's Health, a prospective questionnaire-based study of a nationally representative sample

of 91,642 children (range, 0-17 years). RESULTS: The prevalence of childhood eczema was

12.97% (95% confidence interval [95% CI], 12.42-13.53); 67.0% (95% CI, 64.8-69.2) had mild disease, 26.0% (95% CI, 23.9-28.1) had moderate disease, and 7.0% (95% CI, 5.8-8.3) had

severe disease. There was significant statewide variation of the distribution of eczema severity

(Rao-Scott chi, $P = 0.004$), with highest rates of severe disease in Mid-Atlantic and Midwestern

states. In univariate models, eczema severity was increased with older age, African American and

Hispanic race/ethnicity, lower household income, oldest child in the family, home with a single

mother, lower paternal/maternal education level, maternal general health, maternal/paternal

emotional health, dilapidated housing, and garbage on the streets. In multivariate survey logistic

regression models using stepwise and backward selection, moderate-to-severe eczema was

associated with older age, lower household income, and fair or poor maternal health but inversely

associated with birthplace outside the United States. CONCLUSIONS: These data indicate that

environmental and/or lifestyle factors play an important role in eczema severity.

Skalsky, R. L., Olson, K. E., Blair, C. D., Garcia-Blanco, M. A., & Cullen, B. R. (2014). A "microRNA-like" small RNA expressed by dengue virus? *Proceedings of the National Academy of Sciences of the United States of America*,

Slifka, M. K. (2014). Vaccine-mediated immunity against dengue and the potential for long-term protection against disease. *Frontiers in Immunology*, 5, 195.

It is estimated that over 2.5 billion people are at risk for contracting dengue, a virus responsible for 50-390 million infections in addition to thousands of hospitalizations and deaths each year.

There are no licensed vaccines available to combat this pathogen but substantial efforts are

underway to develop live-attenuated, inactivated, and subunit vaccines that will protect against

each of the four serotypes of dengue. Unfortunately, the results of a recent Phase IIb efficacy trial involving a tetravalent live-attenuated chimeric dengue virus vaccine have raised questions with regard to our current understanding of vaccine-mediated immunity to this important flavivirus. Here, we will briefly summarize these vaccination efforts and discuss the importance of informative in vivo models for determining vaccine efficacy and the need to establish a quantitative correlate of immunity in order to predict the duration of vaccine-induced antiviral protection.

Smith, E. L., Bertozzi, C. R., & Beatty, K. E. (2014). An expanded set of fluorogenic sulfatase activity probes. *Chembiochem*,

Fluorogenic probes that are activated by an enzymatic transformation are ideally suited for profiling enzyme activities in biological systems. Here, we describe two fluorogenic enzyme probes, 3-O-methylfluorescein-sulfate and resorufin-sulfate, that can be used to detect sulfatases in mycobacterial lysates. Both probes were validated with a set of commercial sulfatases and used to reveal species-specific sulfatase banding patterns in a gel-resolved assay of mycobacterial lysates. The fluorogenic probes described here are suitable for various assays and provide a starting point for creating new sulfatase probes with improved selectivity for mycobacterial sulfatases. © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Smith, J. S., Lafage, V., Schwab, F. J., Shaffrey, C. I., Protopsaltis, T., Klineberg, E., et al. (2014). Prevalence and type of cervical deformity among 470 adults with throacolumbar deformity. *Spine*,

STRUCTURED ABSTRACT: Study Design. Multicenter, prospective, consecutive case series.Objectives. To assess prevalence and type of cervical deformity among adults with thoracolumbar (TL) deformity and to assess for associations between cervical deformities and different types of TL deformities.Summary of Background Data. Cervical deformity can present concomitantly with TL deformity and have implications for the management of TL deformity.Methods. Multicenter, prospective, consecutive series of adult (age>18) TL deformity patients. Parameters included pelvic tilt (PT), pelvic incidence (PI), lumbar lordosis (LL), C2-C7 sagittal vertical axis (C2-C7SVA), C7-S1SVA and C2-C7 lordosis (CL). Cervical deformity was

defined as $CL > 0$ degrees (cervical kyphosis [CK]) or $C2-C7SVA > 4$ cm (cervical positive sagittal malalignment [CPSM]). Patients were stratified by the SRS-Schwab TL deformity classification, including curve type (N = sagittal deformity, T = thoracic scoliosis, L = lumbar scoliosis, D = T+L scoliosis) and modifier grades: PT (0:30 degrees), C7-S1SVA (0:9.5cm), PI-LL mismatch (0:20 degrees). Results. 470 patients met criteria (mean age = 52yrs). Mean CL and C2-C7SVA were -8 degrees and 3.2cm, respectively. CK and CPSM prevalence were 31% and 29%, respectively, and prevalence of CK and/or CPSM was 53%. CK prevalence differed by curve type (N = 15%, L = 27%, D = 37%, T = 49%; $p < 0.001$); CPSM prevalence did not differ by curve type ($p = 0.19$). Higher PT grades had lower CK prevalence (0 = 40%, + = 27%, ++ = 15%; $p < 0.001$) but greater CPSM prevalence (0 = 23%, + = 28%, ++ = 45%; $p = 0.001$). Similarly, higher SVA grades had lower CK prevalence (0 = 40%, + = 23%, ++ = 11%; $p < 0.001$) but greater CPSM prevalence (0 = 24%, + = 24%, ++ = 48%; $p < 0.001$). Higher PI-LL grades had lower CK prevalence (0 = 35%, + = 31%, ++ = 22%; $p = 0.034$) but no CPSM association ($p = 0.46$). Conclusions. Cervical deformity is highly prevalent (53%) in adult TL deformity. C7-S1SVA, PT, and PI-LL modifiers are associated with cervical deformity prevalence. These findings suggest that TL deformity evaluation should include assessment for concomitant cervical deformity and that further study is warranted to define their potential clinical impact.

Smith, M. W., Ghindilis, A. L., Seoudi, I. A., Smith, K., Billharz, R., & Simon, H. M. (2014). A new restriction endonuclease-based method for highly-specific detection of DNA targets from methicillin-resistant staphylococcus aureus. *PLoS One*, 9(5), e97826.

PCR multiplexing has proven to be challenging, and thus has provided limited means for pathogen genotyping. We developed a new approach for analysis of PCR amplicons based on restriction endonuclease digestion. The first stage of the restriction enzyme assay is hybridization of a target DNA to immobilized complementary oligonucleotide probes that carry a molecular marker, horseradish peroxidase (HRP). At the second stage, a target-specific restriction enzyme is added, cleaving the target-probe duplex at the corresponding restriction site and releasing the HRP marker into solution, where it is quantified colorimetrically. The assay was tested for detection of the methicillin-resistant *Staphylococcus aureus* (MRSA) pathogen, using the *mecA* gene as a target. Calibration curves indicated that the limit of detection for both target

oligonucleotide and PCR amplicon was approximately 1 nM. Sequences of target oligonucleotides were altered to demonstrate that (i) any mutation of the restriction site reduced the signal to zero; (ii) double and triple point mutations of sequences flanking the restriction site reduced restriction to 50-80% of the positive control; and (iii) a minimum of a 16-bp target-probe dsDNA hybrid was required for significant cleavage. Further experiments showed that the assay could detect the *mecA* amplicon from an unpurified PCR mixture with detection limits similar to those with standard fluorescence-based qPCR. Furthermore, addition of a large excess of heterologous genomic DNA did not affect amplicon detection. Specificity of the assay is very high because it involves two biorecognition steps. The proposed assay is low-cost and can be completed in less than 1 hour. Thus, we have demonstrated an efficient new approach for pathogen detection and amplicon genotyping in conjunction with various end-point and qPCR applications. The restriction enzyme assay may also be used for parallel analysis of multiple different amplicons from the same unpurified mixture in broad-range PCR applications.

Snelling, C., Tanchuck-Nipper, M. A., Ford, M. M., Jensen, J. P., Cozzoli, D. K., Ramaker, M. J., et al.

(2014). Quantification of ten neuroactive steroids in plasma in withdrawal seizure-prone and -resistant mice during chronic ethanol withdrawal. *Psychopharmacology*,

RATIONALE: The rapid membrane actions of neuroactive steroids, particularly via an enhancement of gamma-aminobutyric acidA receptors (GABAARs), participate in the regulation of central nervous system excitability. Prior evidence suggests an inverse relationship between endogenous GABAergic neuroactive steroid levels and behavioral changes in excitability during ethanol withdrawal. OBJECTIVES: Previously, we found that ethanol withdrawal significantly decreased plasma allopregnanolone (ALLO) levels, a potent GABAergic neuroactive steroid, and decreased GABAAR sensitivity to ALLO in Withdrawal Seizure-Prone (WSP) but not in Withdrawal Seizure-Resistant (WSR) mice. However, the effect of ethanol withdrawal on levels of other endogenous GABAAR-active steroids is not known. METHODS: After validation of a gas chromatography-mass spectrometry method for the simultaneous quantification of ten neuroactive steroids, we analyzed plasma from control male WSP-1 and WSR-1 mice and during ethanol withdrawal. RESULTS: We quantified levels of nine neuroactive steroids in WSP-1 and WSR-1 plasma; levels of pregnanolone were not detectable. Basal levels of five neuroactive

steroids were higher in WSR-1 versus WSP-1 mice. Ethanol withdrawal significantly suppressed five neuroactive steroids in WSP-1 and WSR-1 mice, including ALLO. CONCLUSIONS: Due to lower basal levels of some GABAAR-active steroids in WSP-1 mice, a withdrawal-induced decrease in WSP-1 mice may have a greater physiological consequence than a similar decrease in WSR-1 mice. Because WSP-1 mice also exhibit a reduction in GABAAR sensitivity to neuroactive steroids during withdrawal, it is possible that the combined decrease in neuroactive steroids and GABAAR sensitivity during ethanol withdrawal in WSP-1 mice represents a neurochemical substrate for severe ethanol withdrawal.

Sochman, J., Peregrin, J. H., Pavcnik, D., Uchida, B. T., Timmermans, H. A., Sedmera, D., et al.

(2014). Reverse endoventricular artificial obturator in tricuspid valve position. experimental feasibility research study. *Physiological Research*, 63(2), 157-165.

The concept of vena contracta space reduction in tricuspid valve position was tested in an animal model. Feasibility of specific artificial obturator body (REMOT) fixed to the right ventricular apex and interacting with tricuspid valve leaflets was evaluated in three different animal studies.

Catheter-based technique was used in three series of experiment in 7 sheep. First acute study was designed for evaluation if the screwing mode of guide wire anchoring to the right ventricular apex is feasible for the whole REMOT body fixing. Longer study was aimed to evaluate stability of the REMOT body in desired position when fixing the screwing wire on its both ends (to the right ventricular apex and to the skin in the neck area). X-ray methods and various morphological methods were used. The third acute study was intended to the REMOT body deployment without any fixing wire. In all of 7 sheep the REMOT was successfully inserted into the right heart cavities and then fixed to the right ventricular apex area. When the REMOT was left in situ more than 6 months it was stable, induced adhesion to the tricuspid valve leaflet and was associated with a specific cell invasion. Releasing of the REMOT from the guiding tools was also successfully verified. Deployment of the obturator body in the aim to reduce the tricuspid valve orifice is feasible and well tolerated in the short and longer term animal model. Specific cell colonization including neovascularization of the obturator body was observed. © 2014 Institute of Physiology v.v.i.

Sokolowski, E., Turina, C. B., Kikuchi, K., Langenau, D. M., & Keller, C. (2014). Proof-of-concept rare cancers in drug development: The case for rhabdomyosarcoma. *Oncogene*, 33(15), 1877-1889.

Rare diseases typically affect fewer than 200 000 patients annually, yet because thousands of rare diseases exist, the cumulative impact is millions of patients worldwide. Every form of childhood cancer qualifies as a rare disease - including the childhood muscle cancer, rhabdomyosarcoma (RMS). The next few years promise to be an exceptionally good era of opportunity for public-private collaboration for rare and childhood cancers. Not only do certain governmental regulation advantages exist, but these advantages are being made permanent with special incentives for pediatric orphan drug-product development. Coupled with a growing understanding of sarcoma tumor biology, synergy with pharmaceutical muscle disease drug-development programs, and emerging publically available preclinical and clinical tools, the outlook for academic-community-industry partnerships in RMS drug development looks promising. © 2014 Macmillan Publishers Limited.

Song, K., Musci, T., & Caughey, A. B. (2014). Author response to letter from song et al. *Journal of Maternal-Fetal and Neonatal Medicine*, 27(9), 972.

Sowa, E. M., Fellers, J. C., Raisinghani, R. S., Cruz, M. R. S., Hidalgo, P. C., Lee, M. S., et al. (2014). Prevalence of substance misuse in new patients in an outpatient psychiatry clinic using a prescription monitoring program. *Primary Care Companion to the Journal of Clinical Psychiatry*, 16(1)

Objective: To investigate the value of a prescription monitoring program in identifying prescription drug misuse among patients presenting to a resident physician outpatient psychiatry clinic at an academic medical center. Method: Participants were 314 new patients aged 18 years or older presenting to the clinic from October 2011 to June 2012. Resident physicians completed a data collection form for each participant using information from the patient interview and from the prescription monitoring program report. Prescription drug misuse was defined as having any 1 of the following 5 criteria in the prescription monitoring program report: (1) filled prescriptions for 2 or more controlled substances, (2) obtained prescriptions from 2 or more providers, (3) obtained early refills, (4) used 3 or more pharmacies, and (5) the prescription monitoring

program report conflicted with the patient's report. Results: At least 1 indicator of prescription drug misuse was found in 41.7% of patients. Over 69% of the patients that the residents believed were misusing prescription drugs actually met 1 of the criteria for prescription drug misuse. The prescription monitoring program report changed the management only 2.2% of the time. Patients with prior benzodiazepine use ($\chi^2_1 = 17.68, P < .001$), prior opioid use ($\chi^2_1 = 19.98, P < .001$), a personality disorder ($\chi^2_1 = 7.22, P < .001$), and chronic pain ($\chi^2_1 = 14.31, P < .001$) had a higher percentage of prescription drug misuse compared to patients without these factors. Conclusions: Using the prescription monitoring program to screen patients with prior benzodiazepine and opioid use, with a personality disorder, and/or with chronic pain may be useful in confirming the suspicion of prescription drug misuse identified at the initial evaluation.

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Spain, J. E., Tuuli, M., Caughey, A. B., Roehl, K. A., Zhao, Q., & Cahill, A. G. (2014). Normal first stage of preterm labor. *American Journal of Perinatology*, 31(4), 315-320.

Objective To compare first-stage labor patterns in women in preterm labor to those in labor at term. Study Design We performed a retrospective cohort study of consecutive women admitted from 2004 to 2008 with viable (≥ 24 weeks) vertex singleton gestations who reached the second stage of labor. Labor curves for preterm and term labor were created using a repeated-measures analysis with polynomial modeling. Interval-censored regression was used to estimate and compare median time of progression of labor. Multivariable analyses were performed to adjust for smoking, obesity (body mass index ≥ 30), induction, and nulliparity. The adjusted model was stratified by parity and induction of labor. Results Of 5,612 consecutive births, 224 were preterm (< 37 weeks) and 5,388 were term (≥ 37 weeks). Preterm first-stage labor progressed significantly faster than term labor (median time 4 to 10 cm: 3.3 hours versus 4.5 hours, $p < 0.01$). When stratified by parity, preterm labor progressed significantly more rapidly than term labor in both nulliparous and multiparous women (median time 4 to 10 cm: 3.7 hours versus 4.9 hours [$p = 0.04$] in nulliparous women and 2.5 hours versus 4.3 hours [$p = 0.01$] in multiparous women). Conclusion Women in preterm labor progress more rapidly through the first stage of labor than women at term. Copyright © 2014 by Thieme Medical Publishers, Inc.

Spellman, P. T., & Gray, J. W. (2014). Detecting cancer by monitoring circulating tumor DNA. *Nature Medicine*, 20(5), 474-475.

Springer, C. S., Jr, Li, X., Tudorica, L. A., Oh, K. Y., Roy, N., Chui, S. Y., et al. (2014). Intratumor mapping of intracellular water lifetime: Metabolic images of breast cancer? *NMR in Biomedicine*, Shutter-speed pharmacokinetic analysis of dynamic-contrast-enhanced (DCE)-MRI data allows evaluation of equilibrium inter-compartmental water interchange kinetics. The process measured here - transcytolemmal water exchange - is characterized by the mean intracellular water molecule lifetime (τ_{wi}). The τ_{wi} biomarker is a true intensive property not accessible by any formulation of the tracer pharmacokinetic paradigm, which inherently assumes it is effectively zero when applied to DCE-MRI. We present population-averaged in vivo human breast whole tumor τ_{wi} changes induced by therapy, along with those of other pharmacokinetic parameters. In responding patients, the DCE parameters change significantly after only one neoadjuvant chemotherapy cycle: while K_{trans} (measuring mostly contrast agent (CA) extravasation) and k_{ep} (CA intravasation rate constant) decrease, τ_{wi} increases. However, high-resolution, $(1 \text{ mm})^2$, parametric maps exhibit significant intratumor heterogeneity, which is lost by averaging. A typical 400 ms τ_{wi} value means a trans-membrane water cycling flux of $10^{13} \text{ H}_2\text{O}$ molecules s^{-1} /cell for a 12 microm diameter cell. Analyses of intratumor variations (and therapy-induced changes) of τ_{wi} in combination with concomitant changes of v_e (extracellular volume fraction) indicate that the former are dominated by alterations of the equilibrium cell membrane water permeability coefficient, P_w , not of cell size. These can be interpreted in light of literature results showing that τ_{wi} changes are dominated by a P_w (active) component that reciprocally reflects the membrane driving P-type ATPase ion pump turnover. For mammalian cells, this is the Na^+ , K^+ -ATPase pump. These results promise the potential to discriminate metabolic and microenvironmental states of regions within tumors in vivo, and their changes with therapy. (c) 2014 The Authors. *NMR in Biomedicine* published by John Wiley & Sons Ltd.

Starmer, A. J., O'Toole, J. K., Rosenbluth, G., Calaman, S., Balmer, D., West, D. C., et al. (2014). Development, implementation, and dissemination of the I-PASS handoff curriculum: A multisite educational intervention to improve patient handoffs. *Academic Medicine : Journal of the*

Association of American Medical Colleges, 89(6), 876-884.

Patient handoffs are a key source of communication failures and adverse events in hospitals. Despite Accreditation Council for Graduate Medical Education requirements for residency training programs to provide formal handoff skills training and to monitor handoffs, well-established curricula and validated skills assessment tools are lacking. Developing a handoff curriculum is challenging because of the need for standardized processes and faculty development, cultural resistance to change, and diverse institution- and unit-level factors. In this article, the authors apply a logic model to describe the process they used from June 2010 to February 2014 to develop, implement, and disseminate an innovative, comprehensive handoff curriculum in pediatric residency training programs as a fundamental component of the multicenter Initiative for Innovation in Pediatric Education-Pediatric Research in Inpatient Settings Accelerating Safe Sign-outs (I-PASS) Study. They describe resources, activities, and outputs, and report preliminary learner outcomes using data from resident and faculty evaluations of the I-PASS Handoff Curriculum: 96% of residents and 97% of faculty agreed or strongly agreed that the curriculum promoted acquisition of relevant skills for patient care activities. They also share lessons learned that could be of value to others seeking to adopt a structured handoff curriculum or to develop large-scale curricular innovations that involve redesigning firmly established processes. These lessons include the importance of approaching curricular implementation as a transformational change effort, assembling a diverse team of junior and senior faculty to provide opportunities for mentoring and professional development, and linking the educational intervention with the direct measurement of patient outcomes.

Stecker, E. C. (2014). How can I recover if you won't let me sleep? *Science Translational Medicine, 6(231)*

Stecker, E. C. (2014). Why the Oregon CCO experiment could founder. *Journal of Health Politics, Policy and Law,*

The most recent Oregon Medicaid experiment is the boldest attempt yet to limit health care spending. Oregon's approach using a Medicaid waiver from the Center for Medicare and Medicaid Services utilizes global payments with two-sided risk at two levels - coordinated care

organizations (CCOs) and the state. Equally important, the Oregon experiment mandates coverage of medical, behavioral and dental health care using flexible coverage, with the locus of delivery innovation focused at the individual CCO level and with financial consequences for quality-of-care metrics. But insightful design alone is insufficient to overcome the vexing challenge of cost containment on a two- to five-year time horizon; well-tuned execution is also necessary. There are a number of reasons that the Oregon CCO model faces an uphill struggle in implementing the envisioned design.

Steckler, N. A., Ervin, A. D., Latteri, M., Wilkins, T., & Young, L. (2014). Listening to oneself: A description of resiliency practices of first-year medical students. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A105-6.

Stevenson, D. K., McGuinness, G. A., Bancroft, J. D., Boyer, D. M., Cohen, A. R., Gilhooly, J. T., et al. (2014). The initiative on subspecialty clinical training and certification (SCTC): Background and recommendations. *Pediatrics*, 133(SUPPL. 2), S53-S57.

Stone, L. A., & Harshbarger, R. J., 3rd. (2014). Orbital necrotizing fasciitis and osteomyelitis caused by arcanobacterium haemolyticum: A case report. *Ophthalmic Plastic and Reconstructive Surgery*, The facial region is infrequently affected by necrotizing infections. Orbital necrotizing infections are even rarer, seen following trauma, local skin infection, and sinusitis. The authors report a unique case of orbital necrotizing fasciitis and osteomyelitis resulting from Arcanobacterium Haemolyticum ethmoid sinusitis. No prior occurrences of Arcanobacterial species orbital necrotizing fasciitis/osteomyelitis have been reported. A 16-year-old boy presented to the ER with a 3-day history of fever, chills, headache, and sinus pressure. CT scan revealed soft tissue swelling of the right orbit, forehead, and ethmoid sinusitis. Within 24 hours of admission, he suffered rapidly progressive swelling and erythema of the right orbit and forehead with diminished visual acuity, despite broad-spectrum antibiotics. Orbital exploration revealed frankly necrotic fascia and periosteum along the superior aspect. Lateral canthotomy, cantholysis, decompression of the optic nerve, and soft tissue debridement with bone biopsy was performed. Operative specimens isolated Arcanobacterium Haemolyticum. Pathologic examination revealed right orbital osteomyelitis.

Streu, R., Hansen, J., Abrahamse, P., & Alderman, A. K. (2014). Professional burnout among US plastic surgeons: Results of a national survey. *Annals of Plastic Surgery*, 72(3), 346-350.

Purpose: Little is known about professional burnout among plastic surgeons. Our purpose is to describe its prevalence among a large national sample of plastic surgeons and identify contributing factors. Methods: A mailed, self-administered survey was sent to 708 plastic surgeons who were randomly sampled from the American Society of Plastic Surgeons national membership (71% response rate). The dependent variable was professional burnout, measured by 3 subscales from the validated Maslach Burnout Inventory-Human Services Survey. "High" scores in either the emotional exhaustion or depersonalization subscale categories predict professional burnout. The independent variables included surgeon sociodemographic and professional characteristics. W2 was used for the bivariate analyses. Results: Nearly one third (29%) of surgeons scored high in subscale categories predictive of professional burnout. Factors associated with high emotional exhaustion scores included surgeon age, 40-50 years ($P = 0.03$); fair/poor physician health ($P = 0.03$); 60 work hours per week ($P = 0.03$); primarily reconstructive practice ($P < 0.01$); private practice ($P = 0.01$); and group practice ($P = 0.02$). Factors associated with high depersonalization scores included fair/poor physician health ($P = 0.01$); ER call ($P < 0.01$); private practice ($P = 0.01$); and group practice ($P = 0.02$). Conclusions: Nearly one third of plastic surgeons have signs of professional burnout. Middle-aged surgeons and those in poor health are most at risk; along with those who have a reconstructive rather than cosmetic practice, long work hours, ER call responsibility, a nonacademic setting, and group as compared to solo practice. These data have important implications for future workforce shortages and health care quality. Copyright © 2012 by Lippincott Williams & Wilkins.

Subramanya, A. R., & Ellison, D. H. (2014). Distal convoluted tubule. *Clinical Journal of the American Society of Nephrology : CJASN*,

The distal convoluted tubule is the nephron segment that lies immediately downstream of the macula densa. Although short in length, the distal convoluted tubule plays a critical role in sodium, potassium, and divalent cation homeostasis. Recent genetic and physiologic studies have greatly expanded our understanding of how the distal convoluted tubule regulates these

processes at the molecular level. This article provides an update on the distal convoluted tubule, highlighting concepts and pathophysiology relevant to clinical practice.

Swanson, C. M., Nielson, C. M., Shrestha, S., Lee, C. G., Barrett-Connor, E., Jans, I., et al. (2014).

Higher 25(OH)D is associated with lower 25(OH)D and 1,25(OH)D. *The Journal of Clinical Endocrinology and Metabolism*, , jc20141069.

Context: Despite common use of supplemental vitamin D2 in clinical practice, the associations of serum vitamin D2 concentrations with other vitamin D metabolites and total vitamin D are unclear. Objective: The aim of the study was to measure vitamin D2 and D3 levels and examine their associations with each other and with total vitamin D. Design: We performed a cross-sectional analysis of 679 randomly selected participants from the Osteoporotic Fractures in Men Study. 25-Hydroxyvitamin D2 [25(OH)D2], 25(OH)D3, 1,25-dihydroxyvitamin D2 [1,25(OH)2D2], and 1,25(OH)2D3 were measured using liquid chromatography-tandem mass spectrometry and were summed to obtain total 25(OH)D and 1,25(OH)2D. Associations between all metabolites (D2, D3, and total levels) were examined using Wilcoxon rank-sum tests and Spearman correlations. Results: 25(OH)D2 and 1,25(OH)2D2 were detectable in 189 (27.8%) and 178 (26.2%) of the men, respectively. Higher 25(OH)D2 levels did not correlate with higher total 25(OH)D ($r = 0.10$; $P = .17$), although median total 25(OH)D was slightly higher in those with detectable vs undetectable 25(OH)D2 (25.8 vs 24.3 ng/mL; $P < .001$). 25(OH)D2 was not positively associated with total 1,25(OH)2D levels ($r = -0.11$; $P = .13$), and median 1,25(OH)2D level was not higher in those with detectable vs undetectable 25(OH)D2. Higher 25(OH)D2 was associated with lower 25(OH)D3 ($r = -0.35$; $P < .001$) and 1,25(OH)2D3 ($r = -0.32$; $P < .001$), with median levels of both D3 metabolites 18-35% higher when D2 metabolites were undetectable. Conclusions: In a cohort of older men, 25(OH)D2 is associated with lower levels of 25(OH)D3 and 1,25(OH)2D3, suggesting that vitamin D2 may decrease the availability of D3 and may not increase calcitriol levels.

Swartz, C. M. (2014). A mechanism of seizure induction by electricity and its clinical implications. *The Journal of ECT*,

A model of ECT seizure induction by rapid kindling is described. The electrical stimulus as a series

of pulses progressively disrupts neuronal cell membranes, with corresponding progressive increases in intracellular concentrations of sodium, calcium, and voltage. Eventually, the intracellular voltage rises to trigger neuronal firing in waves from seizure foci. The quantity of seizure foci produced is expressed by the stimulus charge multiplied by the current cubed. Differences in implications are described between this model and the traditional model that extrapolates from an isolated single neuron undergoing immediate electrical depolarization by a single pulse. Total brain exposure to seizure neurotransmitter release in ECT is analogous to body exposure to medication in drug therapy and may be expressed by a physiological measurement such as electroencephalographic postictal suppression or peak seizure heart rate.

Swartz, C. M. (2014). Postictal agitation syndrome or anxiety symptoms. *The Journal of ECT*,

Sweeney, R. T., McClary, A. C., Myers, B. R., Biscocho, J., Neahring, L., Kwei, K. A., et al. (2014).

Identification of recurrent SMO and BRAF mutations in ameloblastomas. *Nature Genetics*,
Here we report the discovery of oncogenic mutations in the Hedgehog and mitogen-activated protein kinase (MAPK) pathways in over 80% of ameloblastomas, locally destructive odontogenic tumors of the jaw, by genomic analysis of archival material. Mutations in SMO (encoding Smoothed, SMO) are common in ameloblastomas of the maxilla, whereas BRAF mutations are predominant in tumors of the mandible. We show that a frequently occurring SMO alteration encoding p.Leu412Phe is an activating mutation and that its effect on Hedgehog-pathway activity can be inhibited by arsenic trioxide (ATO), an anti-leukemia drug approved by the US Food and Drug Administration (FDA) that is currently in clinical trials for its Hedgehog-inhibitory activity. In a similar manner, ameloblastoma cells harboring an activating BRAF mutation encoding p.Val600Glu are sensitive to the BRAF inhibitor vemurafenib. Our findings establish a new paradigm for the diagnostic classification and treatment of ameloblastomas.

Talano, J. M., Pulsipher, M. A., Symons, H. J., Militano, O., Shereck, E. B., Giller, R. H., et al. (2014).

New frontiers in pediatric allo-SCT. *Bone Marrow Transplantation*,

The inaugural meeting of 'New Frontiers in Pediatric Allogeneic Stem Cell Transplantation' organized by the Pediatric Blood and Transplant Consortium (PBMTTC) was held at the American Society of Pediatric Hematology and Oncology Annual Meeting. This meeting provided an

international platform for physicians and investigators active in the research and utilization of pediatric Allo-SCT in children and adolescents with malignant and non-malignant disease (NMD), to share information and develop future collaborative strategies. The primary objectives of the conference included: (1) to present advances in Allo-SCT in pediatric ALL and novel pre and post-transplant immunotherapy; (2) to highlight new strategies in alternative allogeneic stem cell donor sources for children and adolescents with non-malignant hematological disorders; (3) to discuss timing of immune reconstitution after Allo-SCT and methods of facilitating more rapid recovery of immunity; (4) to identify strategies of utilizing Allo-SCT in pediatric myeloproliferative disorders; (5) to develop diagnostic and therapeutic approaches to hematological complications post pediatric Allo-SCT; (6) to enhance the understanding of new novel cellular therapeutic approaches to pediatric malignant and non-malignant hematological disorders; and (7) to discuss optimizing drug therapy in pediatric recipients of Allo-SCT. This paper will provide a brief overview of the conference. Bone Marrow Transplantation advance online publication, 12 May 2014; doi: 10.1038/bmt.2014.89.

Tan, L., Dickens, J. A., DeMeo, D. L., Miranda, E., Perez, J., Rashid, S. T., et al. (2014). Circulating polymers in α 1-antitrypsin deficiency. *European Respiratory Journal*, 43(5), 1501-1504.

Teo, A. R., Feters, M. D., Stufflebam, K., Tateno, M., Balhara, Y., Choi, T. Y., et al. (2014). Identification of the hikikomori syndrome of social withdrawal: Psychosocial features and treatment preferences in four countries. *The International Journal of Social Psychiatry*,
BACKGROUND: Hikikomori, a form of social withdrawal first reported in Japan, may exist globally but cross-national studies of cases of hikikomori are lacking. AIMS: To identify individuals with hikikomori in multiple countries and describe features of the condition. METHOD: Participants were recruited from sites in India, Japan, Korea and the United States. Hikikomori was defined as a 6-month or longer period of spending almost all time at home and avoiding social situations and social relationships, associated with significant distress/impairment. Additional measures included the University of California, Los Angeles (UCLA) Loneliness Scale, Lubben Social Network Scale (LSNS-6), Sheehan Disability Scale (SDS) and modified Cornell Treatment Preferences Index. RESULTS: A total of 36 participants with hikikomori were identified, with cases detected in

all four countries. These individuals had high levels of loneliness (UCLA Loneliness Scale M = 55.4, SD = 10.5), limited social networks (LSNS-6 M = 9.7, SD = 5.5) and moderate functional impairment (SDS M = 16.5, SD = 7.9). Of them 28 (78%) desired treatment for their social withdrawal, with a significantly higher preference for psychotherapy over pharmacotherapy, in-person over telepsychiatry treatment and mental health specialists over primary care providers. Across countries, participants with hikikomori had similar generally treatment preferences and psychosocial features. CONCLUSION: Hikikomori exists cross-nationally and can be assessed with a standardized assessment tool. Individuals with hikikomori have substantial psychosocial impairment and disability, and some may desire treatment.

Tereshchenko, L. G., Shah, A. J., Li, Y., & Soliman, E. Z. (2014). Electrocardiographic deep terminal negativity of the P wave in V1 and risk of mortality: The national health and nutrition examination survey III. *Journal of Cardiovascular Electrophysiology*,

INTRODUCTION: Deep terminal negativity of P wave in V1 (DTNPV1), defined as negative P prime larger than one small box (1mm, or 0.1mV), could be easily detected by simple visual inspection of the resting 12-lead ECG. The objective of this study was to determine the relationship between DTNPV1 and all-cause-, cardiovascular disease (CVD)-, and ischemic heart disease (IHD) mortality in the National Health and Nutrition Examination Survey III (NHANES III). METHODS AND RESULTS: After exclusion of participants with atrial fibrillation and missing data, DTNPV1 was automatically measured from standard 12-lead ECG in 8,146 participants. Minnesota and Novacode algorithms were used for the determination of major and minor ECG abnormalities. National Death Index was used to identify the date and cause of death. During a median follow-up of 13.8 years, a total of 2,975 deaths (1303 CVD and 742 IHD deaths) occurred. After adjustment for age, gender, race/ethnicity, IHD, heart failure, chronic obstructive pulmonary disease, cancer, diabetes, body mass index, smoking, dyslipidemia, hypertension, use of antihypertensive and lipid-lowering medications, and ECG abnormalities, DTNPV1 was associated with significantly increased risk of all-cause death (HR [95%CI]: 1.30 [1.10, 1.53]; p = 0.002), CVD death (HR [95%CI]: 1.36 [1.08, 1.72]; p = 0.010), and IHD death (HR [95%CI]: 1.36 [1.00, 1.85]; p = 0.047). CONCLUSION: In a large sample of the adult United States population DTNPV1 is independently associated with increased risk of death due to all-cause, CVD, and IHD,

findings suggesting its potential usefulness as a simple marker to identify individuals at risk of poor outcomes. This article is protected by copyright. All rights reserved.

Terker, A. S., Yang, C. L., McCormick, J. A., Meermeier, N. P., Rogers, S. L., Grossmann, S., et al. (2014). Sympathetic stimulation of thiazide-sensitive sodium chloride cotransport in the generation of salt-sensitive hypertension. *Hypertension*, Excessive renal efferent sympathetic nerve activity contributes to hypertension in many circumstances. Although both hemodynamic and tubular effects likely participate, most evidence supports a major role for alpha-adrenergic receptors in mediating the direct epithelial stimulation of sodium retention. Recently, it was reported, however, that norepinephrine activates the thiazide-sensitive NaCl cotransporter (NCC) by stimulating beta-adrenergic receptors. Here, we confirmed this effect and developed an acute adrenergic stimulation model to study the signaling cascade. The results show that norepinephrine increases the abundance of phosphorylated NCC rapidly (161% increase), an effect largely dependent on beta-adrenergic receptors. This effect is not mediated by the activation of angiotensin II receptors. We used immunodissected mouse distal convoluted tubule to show that distal convoluted tubule cells are especially enriched for beta1-adrenergic receptors, and that the effects of adrenergic stimulation can occur ex vivo (79% increase), suggesting they are direct. Because the 2 protein kinases, STE20p-related proline- and alanine-rich kinase (encoded by STK39) and oxidative stress-response kinase 1, phosphorylate and activate NCC, we examined their roles in norepinephrine effects. Surprisingly, norepinephrine did not affect STE20p-related proline- and alanine-rich kinase abundance or its localization in the distal convoluted tubule; instead, we observed a striking activation of oxidative stress-response kinase 1. We confirmed that STE20p-related proline- and alanine-rich kinase is not required for NCC activation, using STK39 knockout mice. Together, the data provide strong support for a signaling system involving beta1-receptors in the distal convoluted tubule that activates NCC, at least in part via oxidative stress-response kinase 1. The results have implications about device- and drug-based treatment of hypertension.

Tibayan, Y., & Cigarroa, J. E. (2014). Revascularization choices for complex coronary artery disease: All is not what it seems. *Coronary Artery Disease*, 25(4), 279-280.

Tseng, D., Kim, J., Warrick, A., Nelson, D., Pukay, M., Beadling, C., et al. (2014). Oncogenic

mutations in melanomas and benign melanocytic nevi of the female genital tract. *Journal of the American Academy of Dermatology*,

BACKGROUND: The genetic heterogeneity of melanomas and melanocytic nevi of the female genital tract is poorly understood. OBJECTIVE: We aim to characterize the frequency of mutations of the following genes: BRAF, NRAS, KIT, GNA11, and GNAQ in female genital tract melanomas. We also characterize the frequency of BRAF mutations in female genital tract melanomas compared with melanocytic nevi. METHODS: Mutational screening was performed on the following female genital tract melanocytic neoplasms: 25 melanomas, 7 benign melanocytic nevi, and 4 atypical melanocytic nevi. RESULTS: Of the 25 female genital tract melanoma specimens queried, KIT mutations were detected in 4 (16.0%), NRAS mutations in 4 (16.0%), and BRAF mutations in 2 (8.0%) samples. Two of the tumors with KIT mutations harbored double mutations in the same exon. No GNAQ or GNA11 mutations were identified among 11 melanomas screened. BRAF V600E mutations were detected in 7 of 7 benign melanocytic genital nevi (100%) and 3 of 4 atypical genital nevi (75%). LIMITATIONS: Our study is limited by the small sample size of this rare subset of melanomas. CONCLUSION: KIT, NRAS, and BRAF mutations are found in a subset of female genital tract melanomas. Screening for oncogenic mutations is important for developing and applying clinical therapies for melanomas of the female genital tract.

Tsikitis, V. L., White, I., Mori, M., Potter, A., Bhattacharyya, A., Hamilton, S. R., et al. (2014).

Differential expression of microRNA-320a, -145, and -192 along the continuum of normal mucosa to high-grade dysplastic adenomas of the colorectum. *American Journal of Surgery*, 207(5), 717-722.

BACKGROUND: MicroRNA (miR)-320a, miR-145, and miR-192 have been shown to play a role in colorectal carcinogenesis and metastasis. We examined if there is a difference in expression during the histologic progression from normal mucosa (NM) to high-grade dysplastic adenomas (HG). METHODS: Genome-wide miRNA expression profiling was performed on 113 colon adenomas. Information included histologic type, tumor grade, location, sex, age, family, and smoking history. A 2-way ANOVA was performed to evaluate the effect of the following factors adjusted for scan dates: location, sex, age, family history, smoking, and histology. RESULTS: The

expression of miR-320a increased; miR-145 and miR-192 expression decreased ($P < .0001$), with higher histologic grade, and were independent of age, sex, family history, and smoking status.

CONCLUSIONS: The miRs studied had statistically significant changes in expression with progression of histologic grade. These changes may signify progression of normal mucosa to HG and potentially serve as early markers for disease progression and differentiating high- from low-risk adenomas.

Urbanski, H. F., Sorwell, K. G., Garyfallou, V. T., Garten, J., Weiss, A., Renner, L., et al. (2014).

Androgen supplementation during aging: Development of a physiologically appropriate protocol. *Rejuvenation Research*, 17(2), 150-153.

Men show an age-related decline in the circulating levels of testosterone (T) and dehydroepiandrosterone sulfate (DHEAS). Consequently, there is interest in developing androgen supplementation paradigms for old men that replicate the hormone profiles of young adults. In the present study, we used old (21-26 years old) male rhesus monkeys as a model to examine the efficacy of an androgen supplementation paradigm that comprised oral T administration (12mg/kg body weight, dissolved in sesame oil/chocolate) in the evening, and two oral DHEA administrations, 3hr apart (0.04mg/kg body weight, dissolved in sesame oil/chocolate) in the morning. After 5 days of repeated hormone supplementation, serial blood samples were remotely collected from each animal hourly across the 24-hr day, and assayed for cortisol, DHEAS, T, 5 α -dihydrotestosterone (DHT), estrone (E1), and 17 β -estradiol (E2). Following androgen supplementation, T levels were significantly elevated and this was associated with a more sustained nocturnal elevation of T's primary bioactive metabolites, DHT and E1 and E2. Plasma DHEAS levels were also significantly elevated after androgen supplementation; DHEAS levels rose in the early morning and gradually declined during the course of the day, closely mimicking the profiles observed in young adults (7-12 years old); in contrast, cortisol levels were unaltered by the supplementation. Together the data demonstrate a non-invasive androgen supplementation paradigm that restores youthful circulating androgen levels in old male primates. Because this paradigm preserves the natural circulating circadian hormone patterns, we predict that it will produce fewer adverse side effects, such as perturbed sleep or cognitive impairment. © Copyright 2014, Mary Ann Liebert, Inc. 2014.

Vaaga, C. E., Borisovska, M., & Westbrook, G. L. (2014). Dual-transmitter neurons: Functional implications of co-release and co-transmission. *Current Opinion in Neurobiology*, 29C, 25-32.

Co-transmission, the ability of a neuron to release multiple transmitters, has long been recognized in selected circuits. However, the release of multiple primary neurotransmitters from a single neuron is only beginning to be appreciated. Here we consider recent examples of co-transmission as well as co-release-the packaging of multiple neurotransmitters into a single vesicle. The properties associated with each mode of release greatly enhance the possible action of such neurons within circuits. The functional importance of dual- (or multi-) transmitter neurons extends beyond actions on postsynaptic receptors, due in part to differential spatial and temporal profiles of each neurotransmitter. Recent evidence also suggests that the dual-transmitter phenotype can be dynamically regulated during development and following injury or disease.

Vaidya, D., Bennett, W. L., Sibley, C. T., Polak, J. F., Herrington, D. M., & Ouyang, P. (2014). Association of parity with carotid diameter and distensibility multi-ethnic study of atherosclerosis. *Hypertension*,

Pregnancy and childbirth are associated with hemodynamic changes and vascular remodeling. It is not known whether parity is associated with later adverse vascular properties such as larger arterial diameter, wall thickness, and lower distensibility. We used baseline data from 3283 women free of cardiovascular disease aged 45 to 84 years enrolled in the population-based Multi-Ethnic Study of Atherosclerosis. Participants self-reported parity status. Ultrasound-derived carotid artery lumen diameters and brachial artery blood pressures were measured at peak-systole and end-diastole. Common carotid intima-media thickness was also measured. Regression models to determine the association of carotid distensibility coefficient, lumen diameter, and carotid intima-media thickness with parity were adjusted for age, race, height, weight, diabetes mellitus, current smoking, blood pressure medication use, and total and high-density lipoprotein cholesterol levels. The prevalence of nulliparity was 18%. In adjusted models, carotid distensibility coefficient was $0.09 \times 10^{-5} \text{ Pa}^{-1}$ lower ($P=0.009$) in parous versus nulliparous women. Among parous women, there was a nonlinear association with the greatest carotid distensibility coefficient seen in women with 2 live births and significantly lower distensibility seen in primiparas ($P=0.04$) or with higher parity >2 ($P=0.005$). No such pattern of association with

parity was found for lumen diameter or carotid intima-media thickness. Parity is associated with lower carotid artery distensibility, suggesting arterial remodeling that lasts beyond childbirth. These long-term effects on the vasculature may explain the association of parity with cardiovascular events later in life.

Valleau, J. C., & Sullivan, E. L. (2014). The impact of leptin on perinatal development and psychopathology. *Journal of Chemical Neuroanatomy*,

Leptin has long been associated with metabolism as it is a critical regulator of both food intake and energy expenditure, but recently, leptin dysregulation has been proposed as a mechanism of psychopathology. This review discusses the evidence supporting a role for leptin in mental health disorders and describes potential mechanisms that may underlie this association. Leptin plays a critical role in pregnancy and in fetal growth and development. Leptin's role and profile during development is examined in available human studies, and the validity of applying studies conducted in animal models to the human population are discussed. Rodents experience a postnatal leptin surge, which does not occur in humans or larger animal models. This suggests that further research using large mammal models, which have a leptin profile across pregnancy and development similar to humans, are of high importance. Maternal obesity and hyperleptinemia correlate with increased leptin levels in the umbilical cord, placenta, and fetus. Leptin levels are thought to impact fetal brain development; likely by activating proinflammatory cytokines that are known to impact many of the neurotransmitter systems that regulate behavior. Leptin is likely involved in behavioral regulation as leptin receptors are widely distributed in the brain, and leptin influences cortisol release, the mesoaccumbens dopamine pathway, serotonin synthesis, and hippocampal synaptic plasticity. In humans, both high and low levels of leptin are reported to be associated with psychopathology. This inconsistency is likely due to differences in the metabolic state of the study populations. Leptin resistance, which occurs in the obese state, may explain how both high and low levels of leptin are associated with psychopathology, as well as the comorbidity of obesity with numerous mental illnesses. Leptin resistance is likely to influence disorders such as depression and anxiety where both high and low leptin levels have been correlated with symptomatology. Schizophrenia is also associated with both low and high leptin levels. However, as anti-psychotics pharmacotherapy induces weight

gain, which elevates leptin levels, drug-naive populations are needed for further studies. Elevated circulating leptin is consistently found in childhood neurodevelopmental disorders including autism spectrum disorders and Rhetts disorder. Further, studies on the impact of leptin and leptin resistance on psychopathology and neurodevelopmental disorders are important directions for future research. Studies examining the mechanisms by which exposure to maternal obesity and hyperleptinemia during fetal development impact brain development and behavior are critical for the health of future generations.

Van Hook, K., Huang, T., & Alumkal, J. J. (2014). Orteronel for the treatment of prostate cancer. *Future Oncology*, *10*(5), 803-811.

Orteronel (also known as TAK-700) is a novel hormonal therapy that is currently in testing for the treatment of prostate cancer. Orteronel inhibits the 17,20 lyase activity of the enzyme CYP17A1, which is important for androgen synthesis in the testes, adrenal glands and prostate cancer cells. Preclinical studies demonstrate that orteronel treatment suppresses androgen levels and causes shrinkage of androgen-dependent organs, such as the prostate gland. Early reports of clinical studies demonstrate that orteronel treatment leads to reduced prostate-specific antigen levels, a marker of prostate cancer tumor burden, and more complete suppression of androgen synthesis than conventional androgen deprivation therapies that act in the testes alone. Treatment with single-agent orteronel has been well tolerated with fatigue as the most common adverse event, while febrile neutropenia was the dose-limiting toxicity in a combination study of orteronel with docetaxel. Recently, the ELM-PC5 Phase III clinical trial in patients with advanced-stage prostate cancer who had received prior docetaxel was unblinded as the overall survival primary end point was not achieved. However, additional Phase III orteronel trials are ongoing in men with earlier stages of prostate cancer. © 2014 Future Medicine Ltd.

Veleva-Rotse, B. O., & Barnes, A. P. (2014). Brain patterning perturbations following PTEN loss. *Frontiers in Molecular Neuroscience*, *7*, 35.

This review will consider the impact of compromised PTEN signaling in brain patterning. We approach understanding the contribution of PTEN to nervous system development by surveying the findings from the numerous genetic loss-of-function models that have been generated as well

as other forms of PTEN inactivation. By exploring the developmental programs influenced by this central transduction molecule, we can begin to understand the molecular mechanisms that shape the developing brain. A wealth of data indicates that PTEN plays critical roles in a variety of stages during brain development. Many of them are considered here including: stem cell proliferation, fate determination, polarity, migration, process outgrowth, myelination and somatic hypertrophy. In many of these contexts, it is clear that PTEN phosphatase activity contributes to the observed effects of genetic deletion or depletion, however recent studies have also ascribed non-catalytic functions to PTEN in regulating cell function. We also explore the potential impact this alternative pool of PTEN may have on the developing brain. Together, these elements begin to form a clearer picture of how PTEN contributes to the emergence of brain structure and binds form and function in the nervous system.

Verbout, N. G., Yu, X., Healy, L. D., Phillips, K. G., Tucker, E. I., Gruber, A., et al. (2014). Thrombin mutant W215A/E217A treatment improves neurological outcome and attenuates central nervous system damage in experimental autoimmune encephalomyelitis. *Metabolic Brain Disease*, Multiple sclerosis (MS) is a neuroinflammatory disease characterized by demyelination and axonal damage of the central nervous system. The pathogenesis of MS has also been linked to vascular inflammation and local activation of the coagulation system, resulting in perivascular fibrin deposition. Treatment of experimental autoimmune encephalomyelitis (EAE), a model of human MS, with antithrombotic and antiinflammatory activated protein C (APC) reduces disease severity. Since recombinant APC (Drotecogin alfa), originally approved for the treatment of severe sepsis, is not available for human MS studies, we tested the hypothesis that pharmacologic activation of endogenous protein C could likewise improve the outcome of EAE. Mice were immunized with murine myelin oligodendrocyte glycoprotein (MOG) peptides and at the onset of EAE symptoms, were treated every other day with either WE thrombin (25 mug/kg; i.v.), a selective recombinant protein C activator thrombin analog, or saline control. Mice were monitored for changes in disease score until euthanized for ex vivo analysis of inflammation. Administration of WE thrombin significantly ameliorated clinical severity of EAE, reduced inflammatory cell infiltration and demyelination, suppressed the activation of macrophages comprising the CD11b + population and reduced accumulation of fibrin (ogen) in the spinal cord. These data suggest that

symptomatic MS may respond to a treatment strategy that involves temporal pharmacological enhancement of endogenous APC generation.

Villasana, L. E., Westbrook, G. L., & Schnell, E. (2014). Neurologic impairment following closed head injury predicts post-traumatic neurogenesis. *Experimental Neurology*,

In the mammalian hippocampus, neurogenesis persists into adulthood, and increased generation of newborn neurons could be of clinical benefit following concussive head injuries. Post-traumatic neurogenesis has been well documented using "open" traumatic brain injury (TBI) models in rodents; however, human TBI most commonly involves closed head injury. Here we used a closed head injury (CHI) model to examine post-traumatic hippocampal neurogenesis in mice. All mice were subjected to the same CHI protocol, and a gross-motor based injury severity score was used to characterize neurologic impairment one hour after the injury. When analyzed 2 weeks later, post-traumatic neurogenesis was significantly increased only in mice with a high degree of transient neurologic impairment immediately after injury. This increase was associated with an early increase in c-fos activity, and subsequent reactive astrogliosis and microglial activation in the dentate gyrus. Our results demonstrate that the initial degree of neurologic impairment after closed head injury predicts the induction of secondary physiologic and pathophysiologic processes, and that animals with severe neurologic impairment early after injury manifest an increase in post-traumatic neurogenesis in the absence of gross anatomic pathology.

Waddell, C. D., Walter, T. J., Pacheco, S. A., Purdy, G. E., & Runyen-Janecky, L. J. (2014). NtrBC and nac contribute to efficient shigella flexneri intracellular replication. *Journal of Bacteriology*,
Shigella flexneri two-component regulatory systems (TCRS) are responsible for sensing changes in environmental conditions and regulating gene expression accordingly. We examined twelve TCRS that were previously uncharacterized for potential roles in S. flexneri growth within the eukaryotic intracellular environment. We demonstrate that the TCRS EvgSA, NtrBC, and RstBA systems are required for wild-type plaque formation in cultured epithelial cells. The phenotype of the NtrBC mutant depended in part on the Nac transcriptional regulator. Microarray analysis was performed to identify S. flexneri genes differentially regulated by the NtrBC system or Nac in the

intracellular environment. Combined, this study contributes to our understanding of the transcriptional regulation necessary for *Shigella* to effectively adapt to the mammalian host cell.

Wahbeh, H., & Oken, B. (2014). Perceived benefit from mindfulness meditation in combat veterans with posttraumatic stress disorder. *Journal of Alternative and Complementary Medicine (New York, N.Y.)*, 20(5), A64-5.

Wang, X., Jia, Y., Spain, R., Potsaid, B., Liu, J. J., Baumann, B., et al. (2014). Optical coherence tomography angiography of optic nerve head and parafovea in multiple sclerosis. *The British Journal of Ophthalmology*,

AIMS: To investigate swept-source optical coherence tomography (OCT) angiography in the optic nerve head (ONH) and parafoveal regions in patients with multiple sclerosis (MS). METHODS:

Fifty-two MS eyes and 21 healthy control (HC) eyes were included. There were two MS subgroups: 38 MS eyes without an optic neuritis (ON) history (MS -ON), and 14 MS eyes with an ON history (MS +ON). The OCT images were captured by high-speed 1050 nm swept-source OCT. The ONH flow index (FI) and parafoveal FI were quantified from OCT angiograms.

RESULTS: The mean ONH FI was 0.160 ± 0.010 for the HC group, 0.156 ± 0.017 for the MS-ON group, and 0.140 ± 0.020 for the MS+ON group. The ONH FI of the MS+ON group was reduced by 12.5% compared to HC eyes ($p=0.004$). A higher percentage of MS+ON eyes had abnormal ONH FI compared to HC patients (43% vs 5%, $p=0.01$). Mean parafoveal FIs were 0.126 ± 0.007 , 0.127 ± 0.010 , and 0.129 ± 0.005 for the HC, MS-ON, and MS +ON groups, respectively, and did not differ significantly among them. The coefficient of variation (CV) of intravisit repeatability and intervisit reproducibility were 1.03% and 4.53% for ONH FI, and 1.65% and 3.55% for parafoveal FI. CONCLUSIONS: Based on OCT angiography, the FI measurement is feasible, highly repeatable and reproducible, and it is suitable for clinical measurement of ONH and parafoveal perfusion. The ONH FI may be useful in detecting damage from ON and quantifying its severity.

Wang, Z., Tebo, B. M., & Giammar, D. E. (2014). Effects of Mn(II) on UO_2 dissolution under anoxic and oxic conditions. *Environmental Science and Technology*, 48(10), 5546-5554.

Groundwater composition and coupled redox cycles can affect the long-term stability of U(IV)

products from bioremediation. The effects of Mn(II), a redox active cation present at uranium-contaminated sites, on UO₂ dissolution in both oxic and anoxic systems were investigated using batch and continuous-flow reactors. Under anoxic conditions Mn(II) inhibited UO₂ dissolution, which was probably due to adsorption of Mn(II) and precipitation of MnCO₃ that decreased exposure of U(IV) surface sites to oxidants. In contrast, Mn(II) promoted UO₂ dissolution under oxic conditions through Mn redox cycling. Oxidation of Mn(II) by O₂ produced reactive Mn species, possibly short-lived Mn(III) in solution or at the surface, that oxidatively dissolved the UO₂ more rapidly than could the O₂ alone. At pH 8 the Mn cycling was such that there was no measurable accumulation of particulate Mn oxides. At pH 9 Mn oxides could be produced and accumulate, while they were continuously reduced by UO₂, with Mn(II) returning to the aqueous phase. With the rapid turnover of Mn in the redox cycle, concentrations of Mn as low as 10 μM could maintain an enhanced UO₂ dissolution rate. The presence of the siderophore desferrioxamine B (a strong Mn(III)-complexing ligand) effectively decoupled the redox interactions of uranium and manganese to suppress the promotional effect of Mn(II). © 2014 American Chemical Society.

Ward, W. K., Castle, J. R., Jacobs, P. G., & Cargill, R. S. (2014). Can glucose be monitored accurately at the site of subcutaneous insulin delivery? *Journal of Diabetes Science and Technology*, 8(3), 568-574.

Because insulin promotes glucose uptake into adipocytes, it has been assumed that during measurement of glucose at the site of insulin delivery, the local glucose level would be much lower than systemic glucose. However, recent investigations challenge this notion. What explanations could account for a reduced local effect of insulin in the subcutaneous space? One explanation is that, in humans, the effect of insulin on adipocytes appears to be small. Another is that insulin monomers and dimers (from hexamer disassociation) might be absorbed into the circulation before they can increase glucose uptake locally. In addition, negative cooperativity of insulin action (a lower than expected effect of very high insulin concentrations) may play a contributing role. Other factors to be considered include dilution of interstitial fluid by the insulin vehicle and the possibility that some of the local decline in glucose might be due to the systemic effect of insulin. With regard to future research, redundant sensing units might be able to

quantify the effects of proximity, leading to a compensatory algorithm. In summary, when measured at the site of insulin delivery, the decline in subcutaneous glucose level appears to be minimal, though the literature base is not large. Findings thus far support (1) the development of integrated devices that monitor glucose and deliver insulin and (2) the use of such devices to investigate the relationship between subcutaneous delivery of insulin and its local effects on glucose. A reduction in the number of percutaneous devices needed to manage diabetes would be welcome. © 2014 Diabetes Technology Society.

Watts, N. B., Smythe, W., Ward, E. G., Dalbotten, D., Green, V., Tano, M., et al. (2014). *Geoscience alliance: Building capacity to use science for sovereignty in native communities* American Geophysical Union.

Weinstock, Y. E., Alava, I., 3rd, & Dierks, E. J. (2014). Pitfalls in determining head and neck surgical margins. *Oral and Maxillofacial Surgery Clinics of North America*, 26(2), 151-162.

Accurate assessment of surgical margins in the head and neck is a challenge. Multiple factors may lead to inaccurate margin assessment such as tissue shrinkage, nonstandardized nomenclature, anatomic constraints, and complex three dimensional specimen orientation. Excision method and standard histologic processing techniques may obscure distance measurements from the tumor front to the normal tissue edge. Arbitrary definitions of what constitutes a "close" margin do not consider the prognostic significance of resection dimensions. In this article we review some common pitfalls in determining margin status in head and neck resection specimens as well as highlight newer techniques of molecular margin assessment.

White, I., Fortino, J., Curti, B., & Vetto, J. (2014). Clinical impact of sentinel lymph node biopsy in patients with thick (>4 mm) melanomas. *American Journal of Surgery*, 207(5), 702-707.

BACKGROUND: The role of sentinel lymph node status (SLNS) in thick melanoma is evolving. The purpose of this study was to determine the prognostic value of SLNS in thick melanoma.

METHODS: A retrospective analysis of 120 prospectively collected clinically node-negative thick melanomas over 5 years was performed. Patient (age/sex) and tumor (thickness, ulceration, SLNS, mitoses, metastases, and recurrence) features were collected. Multivariate analysis was performed using Cox proportional hazard model. RESULTS: Factors predictive of positive SLN

included male sex, ulceration, and high mitoses. Factors associated with positive SLN had higher local-regional recurrence and metastases than negative SLN. SLNS and tumor thickness impacted 5-year disease-free survival (DFS) and overall survival (OS). Positive SLN, ulceration, age, and mitoses were independent predictors of DFS/OS. CONCLUSIONS: Nonulcerated/lower mitoses thick melanomas had lower positive SLN rates. Positive SLN develop recurrence and metastases and have worse OS/DFS. SLNS is an important prognosticator for OS/DFS. Sentinel lymph node biopsy delineates prognostic groups in thick melanomas and can impact management.

Widger, L. R., Jiang, Y., McQuilken, A. C., Yang, T., Siegler, M. A., Matsumura, H., et al. (2014).

Thioether-ligated iron(ii) and iron(iii)-hydroperoxo/alkylperoxo complexes with an H-bond donor in the second coordination sphere. *Dalton Transactions*, 43(20), 7522-7532.

The non-heme iron complexes, [FeII(N3PySR)(CH₃CN)](BF₄)₂ (1) and [FeII(N3PyamideSR)](BF₄)₂ (2), afford rare examples of metastable Fe(iii)-OOH and Fe(iii)-OOtBu complexes containing equatorial thioether ligands and a single H-bond donor in the second coordination sphere. These peroxo complexes were characterized by a range of spectroscopic methods and density functional theory studies. The influence of a thioether ligand and of one H-bond donor on the stability and spectroscopic properties of these complexes was investigated.

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Wilk, M. A., McAllister, J. T., Cooper, R. F., Dubis, A. M., Patitucci, T. N., Summerfelt, P., et al. (2014).

Relationship between foveal cone specialization and pit morphology in albinism. *Investigative Ophthalmology & Visual Science*,

Purpose: Albinism is associated with disrupted foveal development, though inter-subject variability is becoming appreciated. We sought to quantify this variability and examine the relationship between foveal cone specialization and pit morphology in patients with a clinical diagnosis of albinism. Methods: We recruited 32 subjects with a clinical diagnosis of albinism. DNA was obtained from 25 subjects, and known albinism genes were analyzed for mutations. Relative inner and outer segment (IS and OS) lengthening (fovea:perifovea ratio) was determined from manually segmented spectral domain optical coherence tomography (SD-OCT) B-scans. Foveal pit morphology was quantified for 8 subjects from macular SD-OCT volumes.

Nine subjects underwent imaging with adaptive optics scanning light ophthalmoscopy (AOSLO), and cone density was measured. Results: We found mutations in 21 of 25 subjects, including five novel mutations. All subjects lacked complete excavation of inner retinal layers at the fovea, though four subjects had foveal pits with normal diameter and/or volume. Peak cone density and OS lengthening were variable and overlapped with that observed in normal controls. A 5th hyper-reflective band was observed in the outer retina on SD-OCT in the majority of the subjects with albinism. Conclusions: Foveal cone specialization and pit morphology vary greatly in albinism. Normal cone packing was observed in the absence of a foveal pit, suggesting a pit is not required for packing to occur. The degree to which retinal anatomy correlates with genotype or visual function remains unclear, and future examination of larger patient groups will provide important insight on this issue.

Williams, C. D. (2014). Clopidogrel for smokers and aspirin for nonsmokers?: Not so fast. *Clinical Pharmacology and Therapeutics*, 95(6), 585-587.

New data solidify a "smoker's paradox" for clopidogrel, with current smokers appearing to respond better than nonsmokers. However, the clinical implications of this finding are unclear. This Commentary discusses the new data and puts it into clinical context.

Wilson, A. C., Moss, A., Palermo, T. M., & Fales, J. L. (2014). Parent pain and catastrophizing are associated with pain, somatic symptoms, and pain-related disability among early adolescents. *Journal of Pediatric Psychology*, 39(4), 418-426.

Objective To examine associations between parental history of pain and catastrophizing and their adolescent's pain, somatic symptoms, catastrophizing, and disability. Participants included 178 youths aged 11-14 years recruited through public schools. Adolescents completed measures assessing pain characteristics, somatic symptoms, and pain catastrophizing. Parents reported on their own pain, and catastrophizing about their adolescent's pain. About one quarter of the adolescents and two thirds of parents reported having pain. Parent pain was associated with adolescent pain, somatic symptoms, and pain catastrophizing. Parent catastrophizing was a significant predictor of adolescent somatic symptoms and pain-related disability, beyond the contribution of parent pain. Adolescent catastrophizing mediated the association between parent

catastrophizing and adolescent pain-related disability. Parent history of pain and pain-related cognitions may contribute to adolescent risk for chronic pain. © 2013 © The Author 2013.

Wong, V. W., You, F., Januszyk, M., Gurtner, G. C., & Kuang, A. A. (2014). Transcriptional profiling of rapamycin-treated fibroblasts from hypertrophic and keloid scars. *Annals of Plastic Surgery*, 72(6), 711-719.

Excess scar formation after cutaneous injury can result in hypertrophic scar (HTS) or keloid formation. Modern strategies to treat pathologic scarring represent nontargeted approaches that produce suboptimal results. Mammalian target of rapamycin (mTOR), a central mediator of inflammation, has been proposed as a novel target to block fibroproliferation. To examine its mechanism of action, we performed genomewide microarray on human fibroblasts (from normal skin, HTS, and keloid scars) treated with the mTOR inhibitor, rapamycin. Hypertrophic scar and keloid fibroblasts demonstrated overexpression of collagen I and III that was effectively abrogated with rapamycin. Blockade of mTOR specifically impaired fibroblast expression of the collagen biosynthesis genes PLOD, PCOLCE, and P4HA, targets significantly overexpressed in HTS and keloid scars. These data suggest that pathologic scarring can be abrogated via modulation of mTOR pathways in procollagen and collagen processing.

Woodworth, G. E., Chen, E. M., Horn, J. L., & Aziz, M. F. (2014). Efficacy of computer-based video and simulation in ultrasound-guided regional anesthesia training. *Journal of Clinical Anesthesia*,
STUDY OBJECTIVE: To determine the effectiveness of a short educational video and simulation on improvement of ultrasound (US) image acquisition and interpretation skills. DESIGN: Prospective, randomized study. SETTING: University medical center. SUBJECTS: 28 anesthesia residents and community anesthesiologists with varied ultrasound experience were randomized to teaching video with interactive simulation or sham video groups. SUBJECTS: Participants were assessed preintervention and postintervention on their ability to identify the sciatic nerve and other anatomic structures on static US images, as well as their ability to locate the sciatic nerve with US on live models. MAIN RESULTS: Pretest written test scores correlated with reported US block experience (Kendall tau rank $r = 0.47$) and with live US scanning scores ($r = 0.64$). The teaching video and simulation significantly improved scores on the written examination ($P < 0.001$);

however, they did not significantly improve live US scanning skills. CONCLUSIONS: A short educational video with interactive simulation significantly improved knowledge of US anatomy, but failed to improve hands-on performance of US scanning to localize the nerve.

Work Group, Eichenfield, L. F., Tom, W. L., Berger, T. G., Krol, A., Paller, A. S., et al. (2014).

Guidelines of care for the management of atopic dermatitis: Section 2. management and treatment of atopic dermatitis with topical therapies. *Journal of the American Academy of Dermatology*,

Atopic dermatitis is a common and chronic, pruritic inflammatory skin condition that can affect all age groups. This evidence-based guideline addresses important clinical questions that arise in its management. In this second of 4 sections, treatment of atopic dermatitis with nonpharmacologic interventions and pharmacologic topical therapies are reviewed. Where possible, suggestions on dosing and monitoring are given based on available evidence.

Worstell, T., Ahsan, A. D., Cahill, A. G., & Caughey, A. B. (2014). Length of the second stage of labor:

What is the effect of an epidural? *Obstetrics and Gynecology*, 123 Suppl 1, 84S.

INTRODUCTION: We evaluated the length of the second stage of labor in women with and without epidural analgesia to estimate the effect of an epidural. METHODS: This was a retrospective cohort study of 4,605 women without a history of cesarean delivery at a single community hospital. Length of the second stage of labor with and without an epidural was analyzed for nulliparous and multiparous women by median and 95th percentile. Data were stratified by parity. Subanalysis was performed for women with vaginal delivery. Statistical analysis was performed by Wilcoxon rank-sum test. RESULTS: Nulliparous women with epidural had second stage median length 1 hour longer than women without epidural (105 compared with 42 minutes). However, the 95th percentile for second stage length in nulliparous women with epidural compared with without was almost 2 hours longer (338 compared with 221 minutes). In multiparous women, median second stage length with epidural was 16 minutes longer than without (26 compared with 10 minutes), but the 95th percentile was 112 minutes longer (168 compared with 56 minutes). When analyzing for women who had achieved vaginal delivery, the difference in 95th percentile with and without epidural was 95 minutes for nulliparas and 101

minutes for multiparas (). All comparisons had P value $<.001$. (Table is included in full-text article.) CONCLUSIONS: : Even among women who achieve vaginal delivery, the increase in length of second stage in women who received an epidural was greater than 90 minutes in both nulliparous and multiparous women. These data should inform guidelines surrounding the management of the second stage of labor.

Worstell, T., Nardos, R., Gregory, W. T., & Caughey, A. B. (2014). Delivery planning after a third- or fourth-degree perineal laceration. *Obstetrics and Gynecology*, 123 Suppl 1, 83S.

INTRODUCTION: We evaluated the outcomes associated with planning an elective cesarean compared with vaginal delivery for women with a history of obstetric anal sphincter injuries.

METHODS: A decision analytic model was built using TreeAge software to compare offering an elective cesarean delivery or trial of labor in women with a history of obstetric anal sphincter injuries. A theoretical cohort of 75,152 women with past obstetric anal sphincter injuries was assigned to either elective cesarean delivery or trial of labor. Using baseline probabilities from the literature (), outcomes evaluated included maternal death, fecal incontinence, and urinary incontinence (UI). Duration of incontinence was assumed to be 1 year; sensitivity analysis was performed to evaluate these parameters. (Table is included in full-text article.) RESULTS: : In this hypothetical cohort, trial of labor had better outcomes (), including 17 fewer maternal deaths, more than 50,000 fewer cesarean deliveries, and a savings of \$4,000 per pregnancy. Rates of repeat obstetric anal sphincter injuries, UI, and fecal incontinence were varied over reasonable expected ranges, and trial of labor remained favored. When duration of UI and fecal incontinence were varied, trial of labor was favored until duration of 1.75 and 5.3 years, respectively. When UI and fecal incontinence duration was varied only in the arm experiencing repeat obstetric anal sphincter injuries, trial of labor was favored until a threshold of 4.8 years in women with second obstetric anal sphincter injuries. CONCLUSION: Women with a history of obstetric anal sphincter injuries experience more postpartum UI and fecal incontinence. However, the burden of postpartum incontinence is high in general and cesarean delivery is not entirely protective. Because cesarean delivery is a major abdominal surgery with its own complications, including increased maternal death and implications for future deliveries, this model can inform counseling regarding delivery after obstetric anal sphincter injuries.

Wright, A., Sittig, D. F., McGowan, J., Ash, J. S., & Weed, L. L. (2014). Bringing science to medicine:

An interview with Larry Weed, inventor of the problem-oriented medical record. *Journal of the American Medical Informatics Association : JAMIA*,

Larry Weed, MD is widely known as the father of the problem-oriented medical record and inventor of the now-ubiquitous SOAP (subjective/objective/assessment/plan) note, for developing an electronic health record system (Problem-Oriented Medical Information System, PROMIS), and for founding a company (since acquired), which developed problem-knowledge couplers.

However, Dr Weed's vision for medicine goes far beyond software-over the course of his storied career, he has relentlessly sought to bring the scientific method to medical practice and, where necessary, to point out shortcomings in the system and advocate for change. In this oral history, Dr Weed describes, in his own words, the arcs of his long career and the work that remains to be done.

Wu, L., Lalwani, K., Hook, K. A., Almario, B. M., Fu, R., & Edmunds, B. (2014). Respiratory complications associated with ketamine anesthesia for ophthalmic procedures following intraocular pressure measurement in children. *Journal of Anaesthesiology, Clinical Pharmacology*, 30(2), 253-257.

BACKGROUND: We compared respiratory complications (RCs) in children who received intramuscular (IM) versus intravenous (IV) or no ketamine for intraocular pressure (IOP) measurement to test our observation that IM ketamine is associated with higher incidence of RCs. MATERIALS AND METHODS: We analyzed 149 eye examinations under anesthesia with ketamine in 27 patients and 263 non-ketamine examinations under anesthesia in 81 patients using a mixed effects logistic regression model. RESULTS: IM KETAMINE WAS STRONGLY ASSOCIATED WITH INCREASED ODDS OF RCS COMPARED TO NO KETAMINE (ODDS RATIO (OR): 20.23, $P < 0.0001$) and to IV ketamine (OR: 6.78, $P = 0.02$), as were higher American Society of Anesthesiologists (ASA) classification (OR: 2.60, $P = 0.04$), and the use of volatile agents (OR: 3.32, $P = 0.02$). CONCLUSION: Further studies should be conducted to confirm our observation of increased RCs with IM ketamine.

Xuehong, L., Grandy, D. K., & Janowsky, A. J. (2014). Ractopamine, a livestock feed additive, is a full agonist at trace amine-associated receptor 1. *The Journal of Pharmacology and Experimental Therapeutics*,

Ractopamine (RAC) is fed to an estimated 80% of all beef, swine and turkey raised in the United States. It promotes muscle mass development, limits fat deposition and reduces feed consumption. However, it has several undesirable behavioral side effects in livestock, especially pigs, including restlessness, agitation, excessive oral-facial movements and aggressive behavior. Numerous in vitro and in vivo studies suggest RAC's physiological actions begin with its stimulation of beta1 and beta2 adrenergic receptor-mediated signaling in skeletal muscle and adipose tissue, however the molecular pharmacology of RAC's psychoactive effects is poorly understood. Using human cystic fibrosis transmembrane conductance regulator (hCFTR) chloride channels as a sensor for intracellular cAMP we found that RAC and p-Tyramine (TYR) produced concentration-dependent increases in chloride conductance in oocytes co-expressing hCFTR and mouse trace amine associated receptor 1 (mTAAR1), which was completely reversed by the TAAR1-selective antagonist EPPTB. Oocytes co-expressing hCFTR and the human beta2 adrenergic receptor (hbeta2AR) showed no response to RAC or TYR. These studies demonstrate that, contrary to expectations, RAC is not an agonist of the human beta2AR but rather a full agonist for mTAAR1. Since TAAR1-mediated signaling can influence cardiovascular tone and behavior in several animal models, our finding that RAC is a full mTAAR1 agonist supports the idea this novel mechanism of action influences the physiology and behavior of pigs and other species, as well. These findings should stimulate future studies to characterize the pharmacological, physiological and behavioral actions of RAC in humans and other species exposed to this drug.

Ye, W., Xing, Y., Paustian, C., van de Ven, R., Moudgil, T., Hilton, T. L., et al. (2014). Cross-presentation of viral antigens in dribbles leads to efficient activation of virus-specific human memory T cells. *Journal of Translational Medicine*, 12(1)

Background: Autophagy regulates innate and adaptive immune responses to pathogens and tumors. We have reported that autophagosomes derived from tumor cells after proteasome inhibition, DRibbles (Defective ribosomal products in blebs), were excellent sources of antigens

for efficient cross priming of tumor-specific CD8⁺ T cells, which mediated regression of established tumors in mice. But the activity of DRibbles in human has not been reported.

Methods: DRibbles or cell lysates derived from HEK293T or UbiLT3 cell lines expressing cytomegalovirus (CMV) pp65 protein or transfected with a plasmid encoding dominant HLA-A2 restricted CMV, Epstein-Barr virus (EBV), and Influenza (Flu) epitopes (CEF) were loaded onto human monocytes or PBMCs and the response of human CMV pp65 or CEF antigen-specific CD4⁺ and CD8⁺ memory T cells was detected by intracellular staining. The effect of cytokines (GM-CSF, IL-4, IL-12, TNF- α , IFN- α and IFN- γ) TLR agonists (Lipopolysaccharide, Polyinosinic-polycytidylic acid (poly(I:C), M52-CpG, R848, TLR2 ligand) and CD40 ligand on the cross-presentation of antigens contained in DRibbles or cell lysates was explored. Results: In this study we showed that purified monocytes, or human PBMCs, loaded with DRibbles isolated from cells expressing CMV or CEF epitopes, could activate CMV- or CEF-specific memory T cells. DRibbles were significantly more efficient at stimulating CD8⁺ memory T cells compared to cell lysates expressing the same antigenic epitopes. We optimized the conditions for T-cell activation and IFN- γ production following direct loading of DRibbles onto PBMCs. We found that the addition of Poly(I:C), CD40 ligand, and GM-CSF to the PBMCs together with DRibbles significantly increased the level of CD8⁺ T cell responses. Conclusions: DRibbles containing specific viral antigens are an efficient ex vivo activator of human antigen-specific memory T cells specific for those antigens. This function could be enhanced by combining with Poly(I:C), CD40 ligand, and GM-CSF. This study provides proof-of-concept for applying this strategy to activate memory T cells against other antigens, including tumor-specific T cells ex vivo for immunological monitoring and adoptive immunotherapy, and in vivo as vaccines for patients with cancer. © 2014 Ye et al.; licensee BioMed Central Ltd.

Yeh, S., Forooghian, F., & Suhler, E. B. (2014). Implications of the pacific ocular inflammation uveitis epidemiology study. *JAMA : The Journal of the American Medical Association*, 311(18), 1912-1913.

Zane, H. K., Naka, H., Rosconi, F., Sandy, M., Haygood, M. G., & Butler, A. (2014). Biosynthesis of amphi-enterobactin siderophores by *vibrio harveyi* BAA-1116: Identification of a bifunctional

nonribosomal peptide synthetase condensation domain. *Journal of the American Chemical Society*, 136(15), 5615-5618.

The genome of *Vibrio harveyi* BAA-1116 contains a nonribosomal peptide synthetase (NRPS) gene cluster (aebA-F) resembling that for enterobactin, yet enterobactin is not produced. A gene predicted to encode a long-chain fatty acid CoA ligase (FACL), similar to enzymes involved in the biosynthesis of acyl peptides, resides 15 kb away from the putative enterobactin-like biosynthetic gene cluster (aebG). The proximity of this FACL gene to the enterobactin-like synthetase suggested that *V. harveyi* may produce amphiphilic enterobactin-like siderophores. Extraction of the bacterial cell pellet of *V. harveyi* led to the isolation and structure determination of a suite of eight amphi-enterobactin siderophores composed of the cyclic lactone of tris-2,3-dihydroxybenzoyl-L-serine and acyl-L-serine. The FACL knockout mutant, "aebG *V. harveyi*, and the NRPS knockout mutant, "aebF *V. harveyi*, do not produce amphi-enterobactins. The amphi-enterobactin biosynthetic machinery was heterologously expressed in *Escherichia coli* and reconstituted in vitro, demonstrating the condensation domain of AebF has unique activity, catalyzing two distinct condensation reactions. © 2014 American Chemical Society.

Zhou, Q., Chen, P. C., Devaraneni, P. K., Martin, G. M., Olson, E. M., & Shyng, S. L. (2014).

Carbamazepine inhibits ATP-sensitive potassium channel activity by disrupting channel response to MgADP. *Channels (Austin, Tex.)*, 8(4)

In pancreatic beta-cells, KATP channels consisting of Kir6.2 and SUR1 couple cell metabolism to membrane excitability and regulate insulin secretion. Sulfonylureas, insulin secretagogues used to treat type II diabetes, inhibit KATP channel activity primarily by abolishing the stimulatory effect of MgADP endowed by SUR1. In addition, sulfonylureas have been shown to function as pharmacological chaperones to correct channel biogenesis and trafficking defects. Recently, we reported that carbamazepine, an anticonvulsant known to inhibit voltage-gated sodium channels, has profound effects on KATP channels. Like sulfonylureas, carbamazepine corrects trafficking defects in channels bearing mutations in the first transmembrane domain of SUR1. Moreover, carbamazepine inhibits the activity of KATP channels such that rescued mutant channels are unable to open when the intracellular ATP/ADP ratio is lowered by metabolic inhibition. Here, we investigated the mechanism by which carbamazepine inhibits KATP channel activity. We show

that carbamazepine specifically blocks channel response to MgADP. This gating effect resembles that of sulfonylureas. Our results reveal striking similarities between carbamazepine and sulfonylureas in their effects on KATP channel biogenesis and gating and suggest that the 2 classes of drugs may act via a converging mechanism.

Zhu, M., Streiff, C., Panosian, J., Zhang, Z., Song, X., Sahn, D. J., et al. (2014). Regional strain determination and myocardial infarction detection by three-dimensional echocardiography with varied temporal resolution. *Echocardiography (Mount Kisco, N.Y.)*,

BACKGROUND: Three-dimensional echocardiography (3DE) is a promising method for strain determination; however, there are temporal resolution concerns. This study aims to evaluate the feasibility and accuracy of 3DE on longitudinal and circumferential strain (LS, CS) determination and infarction detection under variable frame rates (FR) and "heart rates" (stroke rates [SR]) conditions. METHODS: Latex balloons were sewn into the left ventricle (LV) of 20 freshly harvested pig hearts which were then passively driven by a pulsatile pump apparatus at stroke volumes (SV) 30-70 mL. The hearts were pumped at 2 normal limits of human heart rate. Full-volume data were acquired before and after a simulated myocardial infarction (MI) at the 2 most commonly used FRs. LS and CS values were evaluated against sonomicrometry. RESULTS: Longitudinal strain and CS derived from high FR acquisitions showed statistically superior correlations with sonomicrometry data (LS: $R^2 = 0.85$, CS: $R^2 = 0.84$) than strain values from low FR (LS: $R^2 = 0.78$, CS: $R^2 = 0.76$) (all $P < 0.01$). After MI induction, LS and CS at different FRs were significantly decreased while maintaining excellent correlations with sonomicrometry data (all $P < 0.001$). There is no statistical difference of strain values between different SR acquisitions. CONCLUSION: Three-dimensional wall-motion tracking has the ability to accurately determine regional myocardial deformation and detect MI. Different heart rates within a physiologically relevant range have no effect on 3D strain accuracy. Strain values calculated from higher frame rate acquisitions were found to have a slightly better accuracy.

Zuckerman, K. E., Sinche, B., Mejia, A., Cobian, M., Becker, T., & Nicolaidis, C. (2014). Latino parents' perspectives on barriers to autism diagnosis. *Academic Pediatrics*, 14(3), 301-308.

OBJECTIVE: Latino children are diagnosed with autism spectrum disorders (ASDs) at older ages

and at the point of more severe symptoms. We sought to qualitatively describe community, family, and health care system barriers to ASD diagnosis in Latino children. METHODS: Five focus groups and 4 qualitative interviews were conducted with 33 parents of Latino children previously diagnosed with an ASD. Participants described Latino community perceptions of autism and barriers they experienced during the diagnostic process. Sessions were audiorecorded and transcribed. Transcripts were coded by 2 researchers, and data were analyzed using thematic analysis. RESULTS: Parents reported low levels of ASD information and high levels of mental health and disability stigma in the Latino community. Parents had poor access to care as a result of poverty, limited English proficiency, and lack of empowerment to take advantage of services. Providers sometimes dismissed parents' concerns. The ASD diagnostic process itself was slow, inconvenient, confusing, and uncomfortable for the child. These factors led many parents to normalize their child's early behaviors, deny that a problem existed, and lose trust in the medical system. CONCLUSIONS: Additional educational outreach to Latino families, destigmatization of ASD, streamlining the ASD diagnostic process, and providing additional support to Latino parents of at-risk children may decrease delays in ASD diagnosis among Latino children.

Zuloaga, K. L., Krasnow, S. M., Zhu, X., Zhang, W., Jouihan, S. A., Shangraw, R. E., et al. (2014).

Mechanism of protection by soluble epoxide hydrolase inhibition in type 2 diabetic stroke. *PLoS One*, 9(5), e97529.

Inhibition of soluble epoxide hydrolase (sEH) is a potential target of therapy for ischemic injury. sEH metabolizes neuroprotective epoxyeicosatrienoic acids (EETs). We recently demonstrated that sEH inhibition reduces infarct size after middle cerebral artery occlusion (MCAO) in type 1 diabetic mice. We hypothesized that inhibition of sEH would protect against ischemic injury in type 2 diabetic mice. Type 2 diabetes was produced by combined high-fat diet, nicotinamide and streptozotocin in male mice. Diabetic and control mice were treated with vehicle or the sEH inhibitor t-AUCB then subjected to 60-min MCAO. Compared to chow-fed mice, high fat diet-fed mice exhibited an upregulation of sEH mRNA and protein in brain, but no differences in brain EETs levels were observed between groups. Type 2 diabetic mice had increased blood glucose levels at baseline and throughout ischemia, decreased laser-Doppler perfusion of the MCA territory after reperfusion, and sustained larger cortical infarcts compared to control mice. t-

AUCB decreased fasting glucose levels at baseline and throughout ischemia, improved cortical perfusion after MCAO and significantly reduced infarct size in diabetic mice. We conclude that sEH inhibition, as a preventative treatment, improves glycemic status, post-ischemic reperfusion in the ischemic territory, and stroke outcome in type 2 diabetic mice.