References

Abou-Chebl, A., Zaidat, O. O., Castonguay, A. C., Gupta, R., Sun, C. H., Martin, C. O., et al. (2014). North american SOLITAIRE stent-retriever acute stroke registry: Choice of anesthesia and outcomes. *Stroke; a Journal of Cerebral Circulation, 45*(5), 1396-1401.

BACKGROUND AND PURPOSE: Previous work that predated the availability of the safer stent-retriever devices has suggested that general anesthesia (GA) may have a negative impact on outcomes in patients with acute ischemic stroke undergoing endovascular therapy. METHODS: We reviewed demographic, clinical, procedural (GA versus local anesthesia [LA], etc), and site-adjudicated angiographic and clinical outcomes data from consecutive patients treated with the Solitaire FR device in the investigator-initiated North American SOLITAIRE Stent-Retriever Acute Stroke (NASA) Registry. The primary outcomes were 90-day modified Rankin Scale, mortality, and symptomatic intracranial hemorrhage. RESULTS: A total of 281 patients from 18 centers were enrolled. GA was used in 69.8% (196/281) of patients. Baseline demographic and procedural factors were comparable between the LA and GA groups, except the former demonstrated longer time-to-groin puncture (395.4+/-254 versus 337.4+/-208 min; P=0.04), lower National Institutes of Health Stroke Scale (NIHSS; 16.2+/-5.8 versus 18.8+/-6.9; P=0.002), lower balloon-guide catheter usage (22.4% versus 49.2%; P=0.0001), and longer fluoroscopy times (39.5+/-33 versus 28+/-22.8 min; P=0.008). Recanalization (thrombolysis in cerebral infarction >/=2b; 72.94% versus 73.6%; P=0.9) and rate of symptomatic intracranial hemorrhage (7.1% versus 11.2%; P=0.4) were similar but modified Rankin Scale </=2 was achieved in more LA patients, 52.6% versus 35.6% (odds ratio, 1.4 [1.1-1.8]; P=0.01). In multivariate analysis, hypertension, NIHSS, unsuccessful revascularization, and GA use (odds ratio, 3.3 [1.6-7.1]; P=0.001) were associated with death. When only anterior circulation and elective GA patients were included, there was a persistent difference in good outcomes in favor of LA patients (50.7% versus 35.5%; odds ratio, 1.3 [1.01-1.6]; P=0.04). CONCLUSIONS: The NASA Registry has demonstrated that clinical outcomes and survival are significantly better in patients treated with LA, without increased symptomatic intracranial hemorrhage risk. Future trials should prospectively evaluate the effect of GA on outcomes.

Adamus, G., Choi, D., Raghunath, A., & Schiffman, J. (2013). Significance of anti-retinal autoantibodies in cancer-associated retinopathy with gynecological cancers. *Journal of Clinical & Experimental Ophthalmology*, *4*(6), 307.

BACKGROUND: The presence of autoantibodies (AAbs) is the primary serological indicator of autoimmunity. Cancer-associated retinopathy (CAR) is associated with AAbs and different types of cancer. The goal of the study was to examine the profile of serum autoantibodies in women with gynecological cancers with and without paraneoplastic visual manifestation. METHODS: Retrospective studies of a cohort of 46 women with symptoms of CAR and gynecological tumors, including endometrial, cervical, ovarian, and fallopian tubes, 111 women with similar tumors without symptoms of CAR, and 60 age-matched healthy controls. Presence of serum AAbs and the identity of targeted antigens were performed by western blotting and their significance was evaluated using an Fisher's exact test. RESULTS: The patients with gynecological CAR had the highest proportion of seropositivity (80%), followed by patients with gynecological cancers without CAR (61%) and healthy controls (58%). Differences in recognition frequencies were found for 17 antigens and 5 retinal antigens were frequently targeted: enolase, aldolase C, carbonic anhydrase II, recoverin and GAPDH. The occurrence of anti-glycolytic enzymes was 2-3 times more frequent in CAR and cancer patients than healthy controls. Anti-recoverin AAbs were prevalent in endometrial CAR. Anti-CAII antibodies were not significantly different between groups of women. In this cohort, cancer was diagnosed before the onset of retinopathy with latency from 2 months to 30 years. The discovery of the ovarian and endometrial cancers and manifestation of visual problems often coincided but Fallopian tube carcinoma was found after visual onset. CONCLUSION: New retinal targets were identified for gynecological CAR. Each gynecological-CAR has its own autoantibody profile different from non-CAR profile, implying that a complex autoantibody signature may be more predictable for diagnosis than a singular AAb. Specific anti-retinal AAbs were most prevalent in women with CAR but their profiles were not fully distinguished from cancer controls.

Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew, E. Y., Clemons, T. E., Sangiovanni, J. P., Danis, R. P., Ferris, F. L.,3rd, et al. (2014). Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report no. 3.

*JAMA Ophthalmology*, *132*(2), 142-149.

IMPORTANCE: The Age-Related Eye Disease Study (AREDS) formulation for the treatment of age-related macular degeneration (AMD) contains vitamin C, vitamin E, beta carotene, and zinc with copper. The Age-Related Eye Disease Study 2 (AREDS2) assessed the value of substituting lutein/zeaxanthin in the AREDS formulation because of the demonstrated risk for lung cancer from beta carotene in smokers and former smokers and because lutein and zeaxanthin are important components in the retina. OBJECTIVE: To further examine the effect of lutein/zeaxanthin supplementation on progression to late AMD. DESIGN, SETTING, PARTICIPANTS: The Age-Related Eye Disease Study 2 is a multicenter, double-masked randomized trial of 4203 participants, aged 50 to 85 years, at risk for developing late AMD; 66% of patients had bilateral large drusen and 34% had large drusen and late AMD in 1 eye. INTERVENTIONS: In addition to taking the original or a variation of the AREDS supplement, participants were randomly assigned in a factorial design to 1 of the following 4 groups: placebo; lutein/zeaxanthin, 10 mg/2 mg; omega-3 long-chain polyunsaturated fatty 3 acids, 1.0 g; or the combination. MAIN OUTCOMES AND MEASURE:S Documented development of late AMD by central, masked grading of annual retinal photographs or by treatment history. RESULTS In exploratory analysis of lutein/zeaxanthin vs no lutein/zeaxanthin, the hazard ratio of the development of late AMD was 0.90 (95% CI, 0.82-0.99; P = .04). Exploratory analyses of direct comparison of lutein/zeaxanthin vs beta carotene showed hazard ratios of 0.82 (95% CI, 0.69-0.96; P = .02) for development of late AMD, 0.78 (95% CI, 0.64-0.94; P = .01) for development of neovascular AMD, and 0.94 (95% CI, 0.70-1.26; P = .67) for development of central geographic atrophy. In analyses restricted to eyes with bilateral large drusen at baseline, the direct comparison of lutein/zeaxanthin vs beta carotene showed hazard ratios of 0.76 (95% CI, 0.61-0.96; P = .02) for progression to late AMD, 0.65 (95% CI, 0.49-0.85; P = .002) for neovascular AMD, and 0.98 (95% CI, 0.69-1.39; P = .91) for central geographic atrophy. CONCLUSION AND RELEVANCE: The totality of evidence on beneficial and adverse effects from AREDS2 and other studies suggests that lutein/zeaxanthin could be more appropriate than beta carotene in the AREDS-type supplements. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00345176.

Ahani, A., Wahbeh, H., Miller, M., Nezamfar, H., Erdogmus, D., & Oken, B. (2013). Change in physiological signals during mindfulness meditation. *2013 6th International IEEE EMBS Conference on Neural Engineering, NER 2013,* San Diego, CA. pp. 1378-1381.
Mindfulness meditation (MM) is an inward mental practice, in which a resting but alert state of mind is maintained. MM intervention was performed for a population of older people with high stress levels. This study assessed signal processing methodologies of electroencephalographic (EEG) and respiration signals during meditation and control condition to aid in quantification of the meditative state. EEG and respiration data were collected and analyzed on 34 novice meditators after a 6-week meditation intervention. Collected data were analyzed with spectral analysis and support vector machine classification to evaluate an objective marker for meditation. We observed meditation and control condition differences in the alpha, beta and theta frequency bands. Furthermore, we established a classifier using EEG and respiration signals with a higher accuracy at discriminating between meditation and control conditions than one using the EEG signal only. EEG and respiration based classifier is a viable objective marker for meditation ability. Future studies should quantify different levels of meditation depth and meditation experience using this classifier. Development of an objective physiological meditation marker will allow the mind-body medicine field to advance by strengthening rigor of methods. © 2013 IEEE.

Alexiev, U., & Farrens, D. L. (2014). Fluorescence spectroscopy of rhodopsins: Insights and approaches. *Biochimica Et Biophysica Acta - Bioenergetics, 1837*(5), 694-709.
Fluorescence spectroscopy has become an established tool at the interface of biology, chemistry and physics because of its exquisite sensitivity and recent technical advancements. However, rhodopsin proteins present the fluorescence spectroscopist with a unique set of challenges and opportunities due to the presence of the light-sensitive retinal chromophore. This review briefly summarizes some approaches that have successfully met these challenges and the novel insights they have yielded about rhodopsin structure and function. We start with a brief overview of fluorescence fundamentals and experimental methodologies, followed by more specific discussions of technical challenges rhodopsin proteins present to fluorescence studies. Finally, we end by discussing some of the unique insights that have been gained specifically about visual rhodopsin and its interactions with affiliate proteins through the use of fluorescence spectroscopy.

This article is part of a Special Issue entitled: Retinal Proteins - You can teach an old dog new tricks. © 2013 The Authors.

Allen, A. R., Eilertson, K., Chakraborti, A., Sharma, S., Baure, J., Habdank-Kolaczkowski, J., et al. (2014). Radiation exposure prior to traumatic brain injury induces responses that differ as a function of animal age. *International Journal of Radiation Biology, 90*(3), 214-223.
Purpose: Uncontrolled radiation exposure due to radiological terrorism, industrial accidents or military circumstances is a continuing threat for the civilian population. Age plays a major role in the susceptibility to radiation; younger children are at higher risk of developing cognitive deterioration when compared to adults. Our objective was to determine if an exposure to radiation affected the vulnerability of the juvenile hippocampus to a subsequent moderate traumatic injury. Materials and methods: Three-week-old (juvenile) and eight-week-old young adult C57BL/J6 male mice received whole body cesium-137 (137Cs) irradiation with 4 gray (Gy). One month later, unilateral traumatic brain injury was induced using a controlled cortical impact system. Two months post-irradiation, animals were tested for hippocampus-dependent cognitive performance in the Morris water-maze. After cognitive testing, animals were euthanized and their brains frozen for immunohistochemical assessment of activated microglia and neurogenesis in the hippocampal dentate gyrus. Results: All animals were able to learn the water maze task; however, treatment effects were seen when spatial memory retention was assessed. Animals that received irradiation as juveniles followed by a moderate traumatic brain injury one month later did not show spatial memory retention, i.e., were cognitively impaired. In contrast, all groups of animals that were treated as adults showed spatial memory retention in the probe trials. Conclusion: Although the mechanisms involved are not clear, our results suggest that irradiation enhanced a young animal's vulnerability to develop cognitive injury following a subsequent traumatic injury. © 2014 Informa UK, Ltd.

Allen, R. H., Micks, E., & Edelman, A. (2013). Pain relief for obstetric and gynecologic ambulatory procedures. *Obstetrics and Gynecology Clinics of North America, 40*(4), 625-645.
As minor gynecologic procedures move from the operating room to the office, providers need to ensure that patients are comfortable and that procedures are performed safely. Although local

anesthesia is commonly used for gynecologic procedures, a multimodal approach may be more effective. If necessary, sedation can be safely provided in an office setting with the correct tools and training. This article reviews evidence-based approaches to pain management for gynecologic procedures in the ambulatory setting. © 2013 Elsevier Inc.

Allison, K. H., Reisch, L. M., Carney, P. A., Weaver, D. L., Schnitt, S. J., O'Malley, F. P., et al. (2014). Understanding diagnostic variability in breast pathology: Lessons learned from an expert consensus review panel. *Histopathology*,

Aims: To gain a better understanding of the reasons for diagnostic variability, with the aim of reducing the phenomenon. Methods and results: In preparation for a study on the interpretation of breast specimens (B-PATH), a panel of three experienced breast pathologists reviewed 336 cases to develop consensus reference diagnoses. After independent assessment, cases coded as diagnostically discordant were discussed at consensus meetings. By the use of qualitative data analysis techniques, transcripts of 16 h of consensus meetings for a subset of 201 cases were analysed. Diagnostic variability could be attributed to three overall root causes: (i) pathologist-related; (ii) diagnostic coding/study methodology-related; and (iii) specimen-related. Most pathologist-related root causes were attributable to professional differences in pathologists' opinions about whether the diagnostic criteria for a specific diagnosis were met, most frequently in cases of atypia. Diagnostic coding/study methodology-related root causes were primarily miscategorizations of descriptive text diagnoses, which led to the development of a standardized electronic diagnostic form (BPATH-Dx). Specimen-related root causes included artefacts, limited diagnostic material, and poor slide quality. After re-review and discussion, a consensus diagnosis could be assigned in all cases. Conclusions: Diagnostic variability is related to multiple factors, but consensus conferences, standardized electronic reporting formats and comments on suboptimal specimen quality can be used to reduce diagnostic variability. © 2014 John Wiley & Sons Ltd.

Alt, J. A., Sautter, N. B., Mace, J. C., Detwiller, K. Y., & Smith, T. L. (2014). Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: A pilot study. *Laryngoscope*, *124*(4), E107-E114.

Objectives/Hypothesis Sleep disturbance, reduced quality of life (QOL), and other components of "sickness behavior" in patients with chronic rhinosinusitis (CRS) are poorly understood. These complex changes in central behavior are due to the effects of immune mediators acting in the brain. We hypothesized that immune mediators that have been associated with CRS are also associated with sickness behavior, somnifacient complaints, and CRS disease-specific QOL. Study Design Pilot study. Methods Twenty patients with CRS were prospectively enrolled and completed the Pittsburgh Sleep Quality Index (PSQI), disease-specific QOL, and olfactory instruments. Ethmoid mucosa was obtained and reverse transcription-polymerase chain reaction was performed for the cytokines interleukin (IL)-4, -13, and transforming growth factor-β (TGF-β). Average change in crossover threshold was calculated, and differences in gene expression were correlated with sleep quality, CRS-specific QOL, and disease severity. Results Patients with CRS reported overall poor sleep quality and poor CRS-specific QOL with significant correlations between them. Increased expression of TGF-β (r = -0.443; P =.050) and IL-4 (r = -0.548; P =.012) correlated with sleep dysfunction, whereas IL-13 expression was linearly associated with worse sleep quality (PSQI scores r = -0.417; P =.075). IL-4 and TGF-β expression was not associated with CRS disease severity or QOL, whereas significantly higher levels of IL-13 expression correlated with worse CRS disease severity and QOL. Conclusions Patients with CRS exhibited behavioral changes commonly referred to as sickness behavior, which include poor sleep quality and reduced QOL. The upregulation of IL-4 and TGF-β may contribute to inflammatory brain-mediated effects on sleep quality, whereas IL-13 may be a pleiotropic signaling molecule influencing sleep, QOL, and CRS disease severity. Level of Evidence 2b. Laryngoscope, 124:E107-E114, 2014 © 2013 The American Laryngological, Rhinological and Otological Society, Inc.

Ambert, K. H., & Cohen, A. M. (2012). k-information gain scaled nearest neighbors: A novel approach to classifying protein-protein interaction-related documents. *IEEE/ACM Transactions on Computational Biology and Bioinformatics / IEEE, ACM, 9*(1), 305-310.

Although publicly accessible databases containing protein-protein interaction (PPI)-related information are important resources to bench and in silico research scientists alike, the amount of time and effort required to keep them up to date is often burdonsome. In an effort to help

identify relevant PPI publications, text-mining tools, from the machine learning discipline, can be applied to help in this process. Here, we describe and evaluate two document classification algorithms that we submitted to the BioCreative II.5 PPI Classification Challenge Task. This task asked participants to design classifiers for identifying documents containing PPI-related information in the primary literature, and evaluated them against one another. One of our systems was the overall best-performing system submitted to the challenge task. It utilizes a novel approach to k-nearest neighbor classification, which we describe here, and compare its performance to those of two support vector machine-based classification systems, one of which was also evaluated in the challenge task.

Ambert, K. H., Cohen, A. M., Burns, G. A. P. C., Boudreau, E., & Sonmez, K. (2013). Finna: A paragraph prioritization system for biocuration in the neurosciences. *2013 AAAI Fall Symposium*, Arlington, VA. , *FS-13-01.* pp. 2-7.

The emphasis of multilevel modeling techniques in the neurosciences has led to an increased need for large-scale, computationally-accessible databases containing neuroscientific data. Despite this, such databases are not being populated at a rate commensurate with their demand amongst Neuroinformaticians. The reasons for this are common to scientific database curation in general, namely, limitation of resources. Much of neuroscience's long tradition of research has been documented in computationally inaccessible formats, such as the pdf, making large-scale data extraction laborious and expensive. Here, we present a system for alleviating one bottleneck in the workflow for curating a typical knowledge base of neuroscience-related information. Finna is designed to rank-order the composite paragraphs of a publication that is predicted to contain information relevant to a knowledge base, in terms of the probability that each documents relevant data. We were able to achieve excellent performance with our classifier (AUC > 0.90) on our manually-curated neuroscience document corpus. Our approach would allow curators to read only a median of 2 paragraphs for each document, in order to identify information relevant to a neuron-related knowledge base. To our knowledge, this is the first system of its kind, and will be a useful baseline for developing similar resources for the neurosciences, and curation in general.

Anacker, A. M., Ahern, T. H., Hostetler, C. M., Dufour, B. D., Smith, M. L., Cocking, D. L., et al. (2014). Drinking alcohol has sex-dependent effects on pair bond formation in prairie voles. *Proceedings of the National Academy of Sciences of the United States of America, 111*(16), 6052-6057.

Alcohol use and abuse profoundly influences a variety of behaviors, including social interactions. In some cases, it erodes social relationships; in others, it facilitates sociality. Here, we show that voluntary alcohol consumption can inhibit male partner preference (PP) formation (a laboratory proxy for pair bonding) in socially monogamous prairie voles (Microtus ochrogaster). Conversely, female PP is not inhibited, and may be facilitated by alcohol. Behavior and neurochemical analysis suggests that the effects of alcohol on social bonding are mediated by neural mechanisms regulating pair bond formation and not alcohol's effects on mating, locomotor, or aggressive behaviors. Several neuropeptide systems involved in the regulation of social behavior (especially neuropeptide Y and corticotropin-releasing factor) are modulated by alcohol drinking during cohabitation. These findings provide the first evidence to our knowledge that alcohol has a direct impact on the neural systems involved in social bonding in a sex-specific manner, providing an opportunity to explore the mechanisms by which alcohol affects social relationships.

Arttamangkul, S., Birdsong, W., & Williams, J. T. (2014). Does PKC activation increase the homologous desensitization of mu opioid receptor? *British Journal of Pharmacology,*

BACKGROUND AND PURPOSE: This study examined the role of agents known to activate protein kinase C on morphine induced desensitization of mu-opioid receptors (MOPr) in brain slices containing locus coeruleus neurons. EXPERIMENTAL APPROACH: Intracellular recordings from rat LC neurons. Two measures were used to characterize desensitization, the decline in the hyperpolarization during the application of a saturating concentration of agonist (acute desensitization) and the decrease in hyperpolarization induced by a sub-saturating concentration of ME following washout of the saturating concentration (sustained desensitization). Internalization of MOPr was studied in brain slices prepared from transgenic mice expressing Flag-MOPrs. The subcellular distribution of activated PKC was examined using a novel fluorescent sensor of PKC in HEK293 cells. KEY RESULTS: The phorbol esters (PMA and PDBu) and muscarine increased acute desensitization induced by a saturating concentration of morphine and ME. These

effects were not sensitive to staurosporine. Staurosporine did not block the decline caused by muscarine. PDBU and muscarine did not affect sustained desensitization induced by ME nor did phorbol esters or muscarine change the trafficking of MOPrs induced by morphine or ME. The distribution of activated PKC measured in HEK293 cells differed depending on which phorbol ester was applied. CONCLUSIONS AND IMPLICATIONS: This study demonstrates a distinct difference in two measures that are often used to measure desensitization. The measure of decline correlated well with the reduction in peak amplitudes caused by PKC activators implicating the modification at other factors rather than MOPr.

Aslam, M. I., Abraham, J., Mansoor, A., Druker, B. J., Tyner, J. W., & Keller, C. (2014). PDGFRbeta reverses EphB4 signaling in alveolar rhabdomyosarcoma. *Proceedings of the National Academy of Sciences of the United States of America, 111*(17), 6383-6388.

Alveolar rhabdomyosarcoma (aRMS) is an aggressive myogenic childhood malignancy, not infrequently presenting as incurable metastatic disease. To identify therapeutic targets, we performed an unbiased tyrosine kinome RNA interference screen in primary cell cultures from a genetically engineered, conditional mouse model of aRMS. We identified ephrin receptor B4 (EphB4) as a target that is widely expressed in human aRMS and that portends a poor clinical outcome in an expression level-dependent manner. We also uncovered cross-talk of this ephrin receptor with another receptor tyrosine kinase, PDGFRbeta, which facilitates PDGF ligand-dependent, ephrin ligand-independent activation of EphB4 converging on the Akt and Erk1/2 pathways. Conversely, EphB4 activation by its cognate ligand, EphrinB2, did not stimulate PDGFRbeta; instead, apoptosis was paradoxically induced. Finally, we showed that small-molecule inhibition of both PDGFRbeta and EphB4 by dasatinib resulted in a significant decrease in tumor cell viability in vitro, as well as decreased tumor growth rate and significantly prolonged survival in vivo. To our knowledge, these results are the first to identify EphB4 and its cross-talk with PDGFRbeta as unexpected vital determinants of tumor cell survival in aRMS, with EphB4 at the crux of a bivalent signaling node that is either mitogenic or proapoptotic.

Asquith, M., Pasala, S., Engelmann, F., Haberthur, K., Meyer, C., Park, B., et al. (2014). Chronic ethanol consumption modulates growth factor release, mucosal cytokine production, and

MicroRNA expression in nonhuman primates. *Alcoholism: Clinical and Experimental Research*, *38*(4), 980-993.

Background: Chronic alcohol consumption has been associated with enhanced susceptibility to both systemic and mucosal infections. However, the exact mechanisms underlying this enhanced susceptibility remain incompletely understood. Methods: Using a nonhuman primate model of ethanol (EtOH) self-administration, we examined the impact of chronic alcohol exposure on immune homeostasis, cytokine, and growth factor production in peripheral blood, lung, and intestinal mucosa following 12 months of chronic EtOH exposure. Results: EtOH exposure inhibited activation-induced production of growth factors hepatocyte growth factor (HGF), granulocyte colony-stimulating factor (G-CSF), and vascular-endothelial growth factor (VEGF) by peripheral blood mononuclear cells (PBMC). Moreover, EtOH significantly reduced the frequency of colonic Th1 and Th17 cells in a dose-dependent manner. In contrast, we did not observe differences in lymphocyte frequency or soluble factor production in the lung of EtOH-consuming animals. To uncover mechanisms underlying reduced growth factor and Th1/Th17 cytokine production, we compared expression levels of microRNAs in PBMC and intestinal mucosa. Our analysis revealed EtOH-dependent up-regulation of distinct microRNAs in affected tissues (miR-181a and miR-221 in PBMC; miR-155 in colon). Moreover, we were able to detect reduced expression of the transcription factors STAT3 and ARNT, which regulate expression of VEGF, G-CSF, and HGF and contain targets for these microRNAs. To confirm and extend these observations, PBMC were transfected with either mimics or antagomirs of miR-181 and miR-221, and protein levels of the transcription factors and growth factors were determined. Transfection of microRNA mimics led to a reduction in both STAT3/ARNT as well as VEGF/HGF/G-CSF levels. The opposite outcome was observed when microRNA antagomirs were transfected. Conclusions: Chronic EtOH consumption significantly disrupts both peripheral and mucosal immune homeostasis, and this dysregulation may be mediated by changes in microRNA expression. © 2013 by the Research Society on Alcoholism.

Atiani, S., David, S. V., Elgueda, D., Locastro, M., Radtke-Schuller, S., Shamma, S. A., et al. (2014). Emergent selectivity for task-relevant stimuli in higher-order auditory cortex. *Neuron*, *82*(2), 486-499.

A variety of attention-related effects have been demonstrated in primary auditory cortex (A1). However, an understanding of the functional role of higher auditory cortical areas in guiding attention to acoustic stimuli has been elusive. We recorded from neurons in two tonotopic cortical belt areas in the dorsal posterior ectosylvian gyrus (dPEG) of ferrets trained on a simple auditory discrimination task. Neurons in dPEG showed similar basic auditory tuning properties to A1, but during behavior we observed marked differences between these areas. In the belt areas, changes in neuronal firing rate and response dynamics greatly enhanced responses to target stimuli relative to distractors, allowing for greater attentional selection during active listening. Consistent with existing anatomical evidence, the pattern of sensory tuning and behavioral modulation in auditory belt cortex links the spectrotemporal representation of the whole acoustic scene in A1 to a more abstracted representation of task-relevant stimuli observed in frontal cortex.

Avila, R., Krishnan, K., Helba, B., Yankelevitz, D., & Hanson, E. (2013). A new platform for quantitative CT imaging dose optimization. *Quantitative Medical Imaging, QMI 2013,* Arlington, VA.

We propose a new set of calibration tools for achieving personalized CT dose optimization in quantitative imaging studies. Small dosimeters placed with a compact CT phantom offers insight into dose and image quality tradeoffs. © OSA 2013.

Back, S. A., & Rosenberg, P. A. (2014). Pathophysiology of glia in perinatal white matter injury. *Glia,*

Injury to the preterm brain has a particular predilection for cerebral white matter. White matter injury (WMI) is the most common cause of brain injury in preterm infants and a major cause of chronic neurological morbidity including cerebral palsy. Factors that predispose to WMI include cerebral oxygenation disturbances and maternal-fetal infection. During the acute phase of WMI, pronounced oxidative damage occurs that targets late oligodendrocyte progenitors (pre-OLs). The developmental predilection for WMI to occur during prematurity appears to be related to both the timing of appearance and regional distribution of susceptible pre-OLs that are vulnerable to a variety of chemical mediators including reactive oxygen species, glutamate, cytokines, and adenosine. During the chronic phase of WMI, the white matter displays abberant regeneration and repair responses. Early OL progenitors respond to WMI with a rapid robust proliferative

response that results in a several fold regeneration of pre-OLs that fail to terminally differentiate along their normal developmental time course. Pre-OL maturation arrest appears to be related in part to inhibitory factors that derive from reactive astrocytes in chronic lesions. Recent high field magnetic resonance imaging (MRI) data support that three distinct forms of chronic WMI exist, each of which displays unique MRI and histopathological features. These findings suggest the possibility that therapies directed at myelin regeneration and repair could be initiated early after WMI and monitored over time. These new mechanisms of acute and chronic WMI provide access to a variety of new strategies to prevent or promote repair of WMI in premature infants. GLIA 2014.

Backus, D., Cordo, P., Gillott, A., Kandilakis, C., Mori, M., & Raslan, A. M. (2014). Assisted movement with proprioceptive stimulation reduces impairment and restores function in incomplete spinal cord injury. *Archives of Physical Medicine and Rehabilitation*,

OBJECTIVE: To test whether, in people with incomplete tetraplegia, treatment combining assisted movement with vibration to the antagonist muscle would reduce impairments and restore upper limb (UL) function. DESIGN: Prospective, pre-post study. SETTING: University lab and non-profit rehabilitation hospital. PARTICIPANTS: We recruited 15 arms from 10 individuals (8 males, mean age 40.5, mean years post-spinal cord injury (SCI) 3) with chronic, incomplete tetraplegia. INTERVENTION: Two to three 20-minute sessions per week over 9 to 13 weeks (25 sessions total) on the AMES device, which combines repeated movement with targeted vibration to the antagonist muscle. MAIN OUTCOME MEASURE(S): Strength and Active Motion Tests on the AMES device; International Standards for the Neurological Classification of SCI (ISNCSCI) motor and 14 sensory exams; Modified Ashworth Scale (MAS); Grasp and Release Test (GRT); Van Lieshout Test (VLT); Capabilities of Upper Extremity questionnaire (CUE). RESULTS: AMES Strength Test scores improved significantly in MCP flexion ($p=0.024$) and extension ($p=0.0067$), and wrist flexion ($p=0.001$) and extension ($p<0.000$). AMES Active Motion scores improved in the hand ($p=0.001$) and wrist ($p=0.001$). The MAS and ISNCSCI scores remained unchanged. GRT scores increased ($p=0.025$). Post-hoc analysis showed a trend from pre- to post-treatment ($p=0.068$), and a significant change from pre-treatment to 3-month follow-up ($p=0.046$). There was no significant change in the VLT ($p=0.951$) or the CUE ($p=0.164$). Five of ten participants reported a

return of 3 sensation to the digits after the first, second or third treatment session. CONCLUSIONS: People with chronic, incomplete tetraplegia may experience improvements 25 in impairments and function after treatment on a device combining assisted movement 6 and proprioceptive stimulation. Further investigation is warranted.

Baker-Groberg, S. M., Cianchetti, F. A., Phillips, K. G., & McCarty, O. J. T. (2014). Development of a method to quantify platelet adhesion and aggregation under static conditions. *Cellular and Molecular Bioengineering*,

Platelets are important players in hemostasis and thrombosis. Thus, accurate assessment of platelet function is crucial for identifying platelet function disorders and measuring the efficacy of antiplatelet therapies. We have developed a novel platelet aggregation technique that utilizes the physical parameter of platelet concentration in conjunction with volume and mass measurements to evaluate platelet adhesion and aggregation. Platelet aggregates were formed by incubating purified platelets on fibrinogen- or fibrillar collagen-coated surfaces at platelet concentrations ranging from 20,000 to 500,000 platelets/μL. Platelets formed aggregates under static conditions in a platelet concentration-dependent manner, with significantly greater mean volume and mass at higher platelet concentrations (≥400,000 platelets/μL). We show that a platelet glycoprotein IIb/IIIa inhibitor abrogated platelet-platelet aggregation, which significantly reduced the volume and mass of the platelets on the collagen surface. This static platelet aggregation technique is amenable to standardization and represents a useful tool to investigate the mechanism of platelet activation and aggregation under static conditions. © 2014 Biomedical Engineering Society.

Baldwin, M. K., & Jensen, J. T. (2014). Health benefits of hormonal contraception. *Maturitas*, *78*(1), 73.

Bellows, C. F., Shadduck, P., Helton, W. S., Martindale, R., Stouch, B. C., & Fitzgibbons, R. (2014). Early report of a randomized comparative clinical trial of strattice™ reconstructive tissue matrix to lightweight synthetic mesh in the repair of inguinal hernias. *Hernia*, *18*(2), 221-230.

Purpose: Biologic grafts are rarely used for inguinal herniorrhaphy. The aim of this study was to compare the clinical outcomes between patients undergoing a Lichtenstein's hernioplasty with a porcine mesh versus a standard synthetic. Methods: A prospective, randomized, double-blinded

multicenter, evaluation of inguinal hernia repair was conducted between 2008 and 2010. Lichtenstein hernioplasty was performed using Strattice™ or lightweight polypropylene (Ultrapro) mesh. Quality of life, pain, overall complication rate, and recurrence were measured. Results: One hundred and seventy-two patients were randomized to Strattice™ (n = 84) or Ultrapro (n = 88). At 3 months postoperatively, there were no differences on the occurrence or type of wound events [RR: 0.98 (95 % CI 0.52-1.86, p = 0.69), Strattice™ (15 events) vs. Ultrapro (16 events)]. The mean level of impairment caused by the hernia, assessed by Activities Assessment Scale (AAS), significantly decreased postoperatively in both groups at 3 months (31 % Strattice™ and 37 % Ultrapro). Patients in the Strattice group reported significantly less postoperative pain during postoperative days 1 through 3 compared to Ultrapro patients. However, the amount of postoperative pain at 3 months, as assessed by the mean worst pain score on a visual analog scale and the Brief Pain Index, was similar between groups (95 % CI 1.0-29.3). No hernia recurrences were observed in either group. Conclusions: Strattice™ is safe and effective in repairing inguinal hernia, with comparable intra-operative and early postoperative morbidity to synthetic mesh. Long-term follow-up is necessary in order to know whether the clinical outcomes of Strattice are equivalent to standard synthetic mesh in patients undergoing Lichtenstein's hernioplasty. © 2013 Springer-Verlag France.

Benninger, B. (2014). Novel femoral artery terminology: Integrating anatomy and clinical procedures leading to standardized intuitive nomenclature. *Clinical Anatomy (New York, N.Y.)*,
The objective of this study is to investigate the terminology of the femoral artery and recommended alternative terminology that satisfies both anatomy and clinical arenas.The femoral artery (FA) is often defined as the continuation of the external iliac artery. Specifically, when the external iliac artery reaches directly beneath the inguinal ligament, it becomes the FA. Currently, Terminologia Anatomica (TA) records the profunda femoris or deep femoral as a terminal branch. Clinicians often use superficial femoral artery (SFA) rather than FA and profunda or deep FA. SFA is actually very deep and well protected for most of its journey. On observation, the terminology in current use is not intuitive. The objective of this study was to investigate the terminology associated with the anatomical and clinical anatomical interpretations of the FA and its terminal branches and to suggest a more appropriate terminology that addresses the points of view of the

macro anatomist, as well as that of the clinician. Literature search was conducted regarding the nomenclature of the FA and its terminal branches. Dissection of 89 embalmed cadavers (49F, 40M, ages 47-89) was conducted to analyze the morphology of the FA and its branches. Perusal of the literature revealed a difference in terminology between anatomical and clinical textbooks/atlases/journals regarding the FA and its terminal branch. Our dissections suggested that the FA may be better defined vis-a-vis its relationship to the anterior and posterior compartments of the thigh. A difference in terminology exists between the anatomical and clinical arenas. A need for a standardized terminology is necessary because clinicians and their publishers have not adopted TA. This study suggests that the current FA be considered the common FA and the continuation of the FA, the SFA be renamed the anterior FA and the current profunda (the deep FA) be renamed the posterior FA, respectively. The proposed terminology mirrors the lower limb anterior/posterior tibial artery terminology. Clin. Anat., 2013. (c) 2013 Wiley Periodicals, Inc.

Benninger, B., Matsler, N., & Delamarter, T. (2014). Classic versus millennial medical lab anatomy. *Clinical Anatomy (New York, N.Y.)*,

This study investigated the integration, implementation, and use of cadaver dissection, hospital radiology modalities, surgical tools, and AV technology during a 12-week contemporary anatomy course suggesting a millennial laboratory. The teaching of anatomy has undergone the greatest fluctuation of any of the basic sciences during the past 100 years in order to make room for the meteoric rise in molecular sciences. Classically, anatomy consisted of a 2-year methodical, horizontal, anatomy course; anatomy has now morphed into a 12-week accelerated course in a vertical curriculum, at most institutions. Surface and radiological anatomy is the language for all clinicians regardless of specialty. The objective of this study was to investigate whether integration of full-body dissection anatomy and modern hospital technology, during the anatomy laboratory, could be accomplished in a 12-week anatomy course. Literature search was conducted on anatomy text, journals, and websites regarding contemporary hospital technology integrating multiple image mediums of 37 embalmed cadavers, surgical suite tools and technology, and audio/visual technology. Surgical and radiology professionals were contracted to teach during the anatomy laboratory. Literature search revealed no contemporary studies

integrating full-body dissection with hospital technology and behavior. About 37 cadavers were successfully imaged with roentograms, CT, and MRI scans. Students were in favor of the dynamic laboratory consisting of multiple activity sessions occurring simultaneously. Objectively, examination scores proved to be a positive outcome and, subjectively, feedback from students was overwhelmingly positive. Despite the surging molecular based sciences consuming much of the curricula, full-body dissection anatomy is irreplaceable regarding both surface and architectural, radiological anatomy. Radiology should not be a small adjunct to understand full-body dissection, but rather, full-body dissection aids the understanding of radiology mediums. The millennial anatomy dissection laboratory should consist of, at least, 50% radiology integration during full-body dissection. This pilot study is an example of the most comprehensive integration of full-body dissection, radiology, and hospital technology. Clin. Anat., 2013. (c) 2013 Wiley Periodicals, Inc.

Berlow, N., Haider, S., Pal, R., & Keller, C. (2013). Quantifying the inference power of a drug screen for predictive analysis. *2013 IEEE International Workshop on Genomic Signal Processing and Statistics*, *GENSIPS 2013*, Houston, TX. pp. 49-52.

A model for drug sensitivity prediction is often inferred from the response of a training drug screen. Quantifying the inference power of perturbations before experimentation will assist in selecting drugs screens with higher predictive power. In this article, we present a novel approach to quantify the inference power of a drug screen based on drug target profiles and biologically motivated monotonicity constraints. We have tested our algorithm on synthetically and experimentally generated datasets and the results illustrate the suitability of the proposed measure in estimating information gained from an experimental drug screen © 2013 IEEE.

Bertagna, X., Pivonello, R., Fleseriu, M., Zhang, Y., Robinson, P., Taylor, A., et al. (2014). LCI699, a potent 11β-hydroxylase inhibitor, normalizes urinary cortisol in patients with cushing's disease: Results from a multicenter, proof-of-concept study. *Journal of Clinical Endocrinology and Metabolism*, *99*(4), 1375-1383.

Introduction: The clinical features and increased mortality associated with Cushing's syndrome result from a chronic excess of circulating cortisol. As LCI699 potently inhibits 11β-hydroxylase,

which catalyzes the final step of cortisol synthesis, it is a potential new treatment for Cushing's disease, the most common cause of endogenous Cushing's syndrome. Methods: Adult patients with moderate-to-severe Cushing's disease (urinary free cortisol [UFC] levels >1.5 X ULN [upper limit of normal]) received oral LCI699 for 10 weeks in this proof-ofconcept study. LCI699 was initiated at 4 mg/d in two equal doses; the dose was escalated every 14 days to 10, 20, 40, and 100 mg/d until UFC normalized, whereupon the dose was maintained until treatment ended (day 70). The primary endpoint was UFC≤ULN or a≥50% decrease from baseline at day 70. Results: Twelve patients were enrolled and completed the study. Baseline UFC ranged over 1.6 - 17.0 X ULN. All 12 patients achieved UFC ≤ ULN or a≥50% decrease from baseline at day 70; 11 (92%) had normal UFC levels at that time. After treatment discontinuation (day 84), UFC was >ULN in 10 patients with available measurements. Mean 11-deoxycortisol, 11-deoxycorticosterone, and adrenocorticotropic hormone levels increased during treatment and declined after discontinuation. Mean systolic and diastolic blood pressure decreased from baseline by 10.0 and 6.0 mmHg, respectively. LCI699 was generally well tolerated; most adverse events (AEs) were mild or moderate. The most common AEs included fatigue (7/12), nausea (5/12), and headache (3/12). No serious drug-related AEs were reported. Conclusions: LCI699 was efficacious and well tolerated in patients with Cushing's disease enrolled in this proof-of-concept study. 

Billeter, A. T., Miller, F. B., Harbrecht, B. G., Bowen, W., Stephens, M. J., Postel, G. C., et al. (2014). Interhospital transfer of blunt multiply injured patients to a level 1 trauma center does not adversely affect outcome. *American Journal of Surgery, 207*(4), 459-466.

BACKGROUND: Stops at nontrauma centers for severely injured patients are thought to increase deaths and costs, potentially because of unnecessary imaging and indecisive/delayed care of traumatic brain injuries (TBIs). METHODS: We studied 754 consecutive blunt trauma patients with an Injury Severity Score greater than 20 with an emphasis on 212 patients who received care at other sites en route to our level 1 trauma center. RESULTS: Referred patients were older, more often women, and had more severe TBI (all $P < .05$). After correction for age, sex, and injury pattern, there was no difference in the type of TBI, Glasgow Coma Scale (GCS) upon arrival at the trauma center, or overall mortality between referred and directly admitted patients.

GCS at the outside institution did not influence promptness of transfer. CONCLUSIONS: Interhospital transfer does not affect the outcome of blunt trauma patients. However, the unnecessarily prolonged stay of low GCS patients in hospitals lacking neurosurgical care is inappropriate.

Black, N. P., Barrett Fromme, H., Maniscalco, J., Ferrell, C., Myers, J., Augustine, E., et al. (2013). *Innovation in patient care and medical resident education: Using blended instruction to transform nighttime patient care from a service model into an educational model* IGI Global.

Medical resident education changed dramatically on July 1, 2011 with the institution of new duty-hour work restrictions. The move to shift scheduling changed the notion of nighttime work from a time of service to one of education. The National Pediatric Nighttime Education Steering Group responded to this paradigm shift by creating a national, peer-reviewed, Web- and case-based curriculum for nighttime learning in pediatrics. Field-test results from implementation in 89 programs revealed statistically significant improvements in knowledge and confidence, but a need for improvement in usability interface, instructional design, and dissemination. Finding support to improve upon the design of the curriculum and provide a robust platform for dissemination and use by residency programs presents a significant challenge, especially in light of severe threats to graduate medical education funding at the national level. 

Bouska, A., McKeithan, T. W., Deffenbacher, K. E., Lachel, C., Wright, G. W., Iqbal, J., et al. (2014). Genome-wide copy-number analyses reveal genomic abnormalities involved in transformation of follicular lymphoma. *Blood, 123*(11), 1681-1690.

Follicular lymphoma (FL), the second most common type of non-Hodgkin lymphoma in the western world, is characterized by the t(14;18) translocation, which is present in up to 90% of cases. We studied 277 lymphoma samples (198 FL and 79 transformed FL [tFL]) using a single-nucleotide polymorphism array to identify the secondary chromosomal abnormalities that drive the development of FL and its transformation to diffuse large B-cell lymphoma. Common recurrent chromosomal abnormalities in FL included gains of 2, 5, 7, 6p, 8, 12, 17q, 18, 21, and X and losses on 6q and 17p. We also observed many frequent small abnormalities, including losses of 1p36.33-p36.31, 6q23.3-q24.1, and 10q23.1-q25.1 and gains of 2p16.1-p15, 8q24.13-

q24.3, and 12q12-q13.13, and identified candidate genes that may be driving this selection. Recurrent abnormalities more frequent in tFL samples included gains of 3q27.3-q28 and chromosome 11 and losses of 9p21.3 and 15q. Four abnormalities, gain of X or Xp and losses of 6q23.2-24.1 or 6q13-15, predicted overall survival. Abnormalities associated with transformation of the disease likely impair immune surveillance, activate the nuclear factor-κB pathway, and deregulate p53 and B-cell transcription factors. Copyright 2011 by The American Society of Hematology; all rights reserved.

Boutros, P. C., Ewing, A. D., Ellrott, K., Norman, T. C., Dang, K. K., Hu, Y., et al. (2014). Global optimization of somatic variant identification in cancer genomes with a global community challenge. *Nature Genetics, 46*(4), 318-319.

Brace, R. A., Anderson, D. F., & Cheung, C. Y. (2014). Ovine fetal swallowing responses to polyhydramnios. *Physiological Reports, 2*(3), e00279.

Abstract Swallowing of amniotic fluid by late gestation fetuses increases when amniotic fluid volume (AFV) is elevated. Our objectives were to quantitatively characterize fetal swallowing when AFV is elevated above normal to polyhydramniotic levels and to explore the mechanisms that mediate these changes. Late gestation fetal sheep were studied under basal conditions and during intra-amniotic infusion of lactated Ringer's solution. Control AFV averaged 631 +/- 214 mL (SE, n = 6), swallowed volume was 299 +/- 94 mL/day, and there were 5.7 +/- 1.8 bouts/day of rapid swallowing. During intra-amniotic infusion, AFV (3065 +/- 894 mL) and daily swallowed volume (699 +/- 148 mL/day) increased ($P < 0.05$) and the number of bouts reached a maximum of 13.7 +/- 2.0 bouts/day when AFV exceeded 1500 mL. Unexpectedly, the volume swallowed per bout (57.3 +/- 5.8 mL, n = 102) did not vary with AFV ($r = 0.023$, $P = 0.81$). Neither the number of swallows/day nor the volume/swallow changed consistently with elevated AFV. Daily swallowed volume increases and reaches a maximum of twice normal as AFV approaches polyhydramniotic levels. Mechanistically, the increase in swallowing was achieved primarily by an increase in the number of bouts of swallowing per day rather than the expected passive increase in volume per bout. This implies changes in fetal behavior as AFV was elevated.

Furthermore, swallowed volume was four times more sensitive to increases in AFV than reported previously.

Brown, D. S., Durkan, M. G., Foss, E. W., Szumowski, J., & Crawford, D. C. (2014). Temporal in vivo assessment of fresh osteochondral allograft transplants to the distal aspect of the femur by dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) and zonal T2 mapping MRI. *The Journal of Bone and Joint Surgery.American Volume*, *96*(7), 564-572.

BACKGROUND: Zonal T2 mapping and dGEMRIC (delayed gadolinium-enhanced magnetic resonance imaging of cartilage) are diagnostic quantitative techniques to evaluate the biochemical health of articular cartilage. We adapted these techniques to investigate the results of osteochondral allograft transplantation and correlated the findings with patient-reported outcomes. METHODS: Nine patients with contained ICRS (International Cartilage Repair Society) grade-4 defects of the articular portion of a femoral condyle were treated with fresh osteochondral allografts and were evaluated prospectively with dGEMRIC and T2 mapping before and after gadolinium administration. The KOOS (Knee Injury Osteoarthritis Outcome Score) and IKDC (International Knee Documentation Committee) subjective scores were obtained at baseline and at one and two years postoperatively. For quantitative T2 mapping, regions of interest were drawn in the deep and superficial layers of allograft and control cartilage. For dGEMRIC analyses, the relaxation rate, post-gadolinium change in relaxation rate, and ratio between changes in the allograft and control regions of interest were calculated from T1 values. RESULTS: The mean ratio between the post-gadolinium changes in the allograft and control cartilage was 1.13 at one year and 1.55 at two years, and the ratio increased in eight of nine patients from one to two years. There was no difference between the mean T2 values in the deep zone of the allograft and control cartilage at one or two years ($p > 0.05$), but mean T2 values were higher in the superficial zone of the allograft cartilage at one ($p < 0.0001$) and two ($p < 0.028$) years. The mean improvement from baseline was significant at one and two years for the IKDC and all five KOOS subdomains ($p < 0.05$). All or nearly all patients showed improvements in all clinical outcomes scores at one year. CONCLUSIONS: Functional MRI techniques can be applied to noninvasively assess the biochemical health of cartilage after osteochondral allograft transplantation. The MRI findings correlated with certain patient-reported outcomes in the early

postoperative period. Relative glycosaminoglycan content and the collagen structure of allograft cartilage may undergo time-dependent degeneration. A patient's perception of clinical outcome and quality of life is likely multifactorial and is impacted by more than the health of the allograft cartilage. LEVEL OF EVIDENCE: Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

Brummer, N. B., Rawson, J. A., Grimm, M. W., Tupper, P., Miller, A. J. L., Billings, C. J., et al. (2013). Electrode selection and other design considerations for a modular, portable single-channel EEG-augmented hearing aid. *2013 6th International IEEE EMBS Conference on Neural Engineering, NER 2013,* San Diego, CA. pp. 431-434.

In this paper, we present a design for a portable single-channel EEG-controlled hearing aid. The design has relevance for future versions of hearing aids that may make use of electroencephalography (EEG) to control the settings and signal processing on the hearing aid. The design also has relevance for auditory-based brain-computer interface (BCI) systems. Current hearing aid technology uses only acoustic information to perform noise removal algorithms and to do directional beamforming using array microphones. Recent advances in EEG and applications in auditory-based BCI have opened the door for the potential use of EEG information to automatically control the function of a hearing aid. In this paper we describe the design of a modular mobile hearing aid platform that accepts EEG inputs. We have investigated which electrodes are the most relevant for performing an EEG-based classifier of oddball sounds using tones and nonsense syllables so that eventually a minimal set of electrodes may be used in a portable auditory-based EEG BCI system. And we have described the modular design of a portable hearing aid system which enables interchange of different USB-enabled EEG electrodes, codecs, and battery supplies. The system includes a dual-microphone array for enabling adaptive beamforming noise cancelation and a Linux-based processor for performing advanced noise cancelation and compression algorithms. 

Bulger, E. M., Maier, R. V., Sperry, J., Joshi, M., Henry, S., Moore, F. A., et al. (2014). A novel drug for treatment of necrotizing soft-tissue infections: A randomized clinical trial. *JAMA Surgery,* IMPORTANCE Necrotizing soft-tissue infections (NSTI) have high morbidity and mortality rates

despite aggressive surgical debridement and antibiotic therapy. AB103 is a peptide mimetic of the T-lymphocyte receptor, CD28. We hypothesized that AB103 will limit inflammatory responses to bacterial toxins and decrease the incidence of organ failure. OBJECTIVES To establish the safety of AB103 in patients with NSTI and evaluate the potential effects on clinically meaningful parameters related to the disease. DESIGN, SETTING, AND PARTICIPANTS A prospective, randomized, placebo-controlled, double-blinded study was performed in 6 academic medical centers in the United States. Participants included adults with NSTI. Of 345 patients screened, 43 were enrolled for the intent-to-treat analysis, and 40 met criteria for the modified intent-to-treat analysis; 15 patients each were included in the high-dose and low-dose treatment arms, and 10 in the placebo arm. INTERVENTION Single intravenous dose of AB103 (0.5 or 0.25 mg/kg) within 6 hours after diagnosis of NSTI. MAIN OUTCOMES AND MEASURES Change in the Sequential Organ Failure Assessment score within 28 days, intensive care unit-free and ventilator-free days, number and timing of debridements, plasma and tissue cytokine levels at 0 to 72 hours, and adverse events. RESULTS Baseline characteristics were comparable in the treatment groups. The Sequential Organ Failure Assessment score improved from baseline in both treatment groups compared with the placebo group at 14 days (change from baseline score, -2.8 in the high-dose, -2 in the low-dose, and +1.3 in the placebo groups; P = .04). AB103-treated patients had a similar number of debridements (mean [SD], 2.2 [1.1] for the high-dose, 2.3 [1.2] for the low-dose, and 2.8 [2.1] for the placebo groups; P = .56). There were no statistically significant differences in intensive care unit-free and ventilator-free days or in plasma and tissue cytokine levels. No drug-related adverse events were detected. CONCLUSIONS AND RELEVANCE AB103 is a safe, promising new agent for modulation of inflammation after NSTI. Further study is warranted to establish efficacy. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01417780.

Burke, R. T., Meadows, S., Loriaux, M. M., Currie, K. S., Mitchell, S. A., Maciejewski, P., et al. (2014). A potential therapeutic strategy for chronic lymphocytic leukemia by combining idelalisib and GS-9973, a novel spleen tyrosine kinase (syk) inhibitor. *Oncotarget*, *5*(4), 908-915.
Agents that target B-cell receptor (BCR) signaling in lymphoid malignancies including idelalisib (GS-1101) and fostamatinib which inhibit the delta isoform of PI3 kinase (PI3Kd) and spleen tyrosine kinase (Syk) respectively have shown significant clinical activity. By disrupting B-cell

signaling pathways, idelalisib treatment has been associated with a dramatic lymph node response, but eradication of disease and relapse in high risk disease remain challenges. Targeting the BCR signaling pathway with simultaneous inhibition of PI3Kd and Syk has not yet been reported. We evaluated the pre-clinical activity of idelalisib combined with the novel and selective Syk inhibitor GS-9973 in primary peripheral blood and bone marrow Chronic Lymphocytic Leukemia (CLL) samples. Both PI3Kd and Syk inhibition reduced CLL survival and in combination induced synergistic growth inhibition and further disrupted chemokine signaling at nanomolar concentrations including in bone marrow derived and poor risk samples. Simultaneous targeting of these kinases may significantly increase clinical activity.

Burney, P., Jithoo, A., Kato, B., Janson, C., Mannino, D., Nizankowska-Mogilnicka, E., et al. (2014). Chronic obstructive pulmonary disease mortality and prevalence: The associations with smoking and poverty-A bold analysis. *Thorax*, *69*(5), 465-473.
Background Chronic obstructive pulmonary disease (COPD) is a commonly reported cause of death and associated with smoking. However, COPD mortality is high in poor countries with low smoking rates. Spirometric restriction predicts mortality better than airflow obstruction, suggesting that the prevalence of restriction could explain mortality rates attributed to COPD. We have studied associations between mortality from COPD and low lung function, and between both lung function and death rates and cigarette consumption and gross national income per capita (GNI). Methods National COPD mortality rates were regressed against the prevalence of airflow obstruction and spirometric restriction in 22 Burden of Obstructive Lung Disease (BOLD) study sites and against GNI, and national smoking prevalence. The prevalence of airflow obstruction and spirometric restriction in the BOLD sites were regressed against GNI and mean pack years smoked.

Burt, B. M., Cameron, R. B., Mollberg, N. M., Kosinski, A. S., Schipper, P. H., Shrager, J. B., et al. (2014). Malignant pleural mesothelioma and the society of thoracic surgeons database: An analysis of surgical morbidity and mortality. *Journal of Thoracic and Cardiovascular Surgery*,
Background: To date, reported surgical morbidity and mortality for pleurectomy/decortication and extrapleural pneumonectomy performed for malignant pleural mesothelioma primarily represent

the experience of a few specialized centers. For comparison, we examined early outcomes of pleurectomy/decortication and extrapleural pneumonectomy from a broader group of centers/surgeons participating in the Society of Thoracic Surgeons-General Thoracic Database. Methods: All patients in the Society of Thoracic Surgeons-General Thoracic Database (version 2.081, representing 2009-2011) who underwent pleurectomy/decortication or extrapleural pneumonectomy for malignant pleural mesothelioma were identified. Patient characteristics, morbidity, mortality, center volume, and procedure were examined using univariable and multivariable analyses. Results: A total of 225 patients underwent pleurectomy/decortication (n = 130) or extrapleural pneumonectomy (n = 95) for malignant pleural mesothelioma at 48 centers. Higher volumes of procedures (≥5/y) were performed at 3 pleurectomy/decortication and 2 extrapleural pneumonectomy centers. Patient characteristics were statistically equivalent between pleurectomy/decortication and extrapleural pneumonectomy groups, except those undergoing extrapleural pneumonectomy were younger (63.2 ± 7.8 years vs 68.3 ± 9.5 years; P < .001) and more likely to have received preoperative chemotherapy (30.1% vs 17.8%; P = .036). Major morbidity was greater after extrapleural pneumonectomy, including acute respiratory distress syndrome (8.4% vs 0.8%; P = .005), reintubation (14.7% vs 2.3%; P = .001), unexpected reoperation (9.5% vs 1.5%; P = .01), and sepsis (4.2% vs 0%; P = .03), as was mortality (10.5% vs 3.1%; P = .03). Multivariate analyses revealed that extrapleural pneumonectomy was an independent predictor of major morbidity or mortality (odds ratio, 6.51; P = .001). Compared with high-volume centers, increased acute respiratory distress syndrome was seen in low-volume centers performing extrapleural pneumonectomy (0% vs 12.5%; P = .05). Conclusions: Extrapleural pneumonectomy is associated with greater morbidity and mortality compared with pleurectomy/decortication when performed by participating surgeons of the Society of Thoracic Surgeons-General Thoracic Database. Effects of center volume require further study. 

Byrd, J. C., Pagel, J. M., Awan, F. T., Forero, A., Flinn, I. W., Deauna-Limayo, D. P., et al. (2014). A phase 1 study evaluating the safety and tolerability of otlertuzumab, an anti-CD37 mono-specific ADAPTIR therapeutic protein in chronic lymphocytic leukemia. *Blood, 123*(9), 1302-1308. Otlertuzumab is a novel humanized anti-CD37 protein therapeutic. This study evaluated the

safety of otlertuzumab administered intravenously to patients with chronic lymphocytic leukemia (CLL). Otlertuzumab was administered weekly for up to 8 weeks followed by 1 dose per month for 4 months ranging from 0.03 to 20 mg/kg in the dose-escalation phase and 10 to 30 mg/kg in the dose-expansion phase. Responses were determined by using the 1996 National Cancer Institute (NCI-96) and 2008 International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria. Fifty-seven patients were treated in the dose-escalation phase and 26 in the dose-expansion phase. A maximum-tolerated dose was not identified. Response occurred in 19 (23%) of 83 treated patients by NCI-96 criteria. All responses were partial and occurred more commonly in patients with symptomatic untreated CLL (6/7) or 1 to 2 prior therapies (12/28) vs 3 or more therapies (1/48). Twenty percent (12/61) with serial computed tomography scan assessment had a response per IWCLL criteria. The most frequent adverse events were infusion reactions, fatigue, nausea, and diarrhea and were not dose related. Otlertuzumab was well tolerated, and modest clinical activity was observed. Otlertuzumab warrants further evaluation in combination with other agents for the treatment of CLL. This trial was registered at www.clinicaltrials.gov as #NCT00614042. © 2014 by The American Society of Hematology.

Cahill, A. G., & Caughey, A. B. (2014). In reply. *Obstetrics and Gynecology*, *123*(4), 887.

Calonge, N., Klein, R. D., Berg, J. S., Campos-Outcalt, D., Djulbegovic, B., Ganiats, T., et al. (2014). Recommendations from the EGAPP working group: Does PCA3 testing for the diagnosis and management of prostate cancer improve patient health outcomes? *Genetics in Medicine*, *16*(4), 338-346.

Summary of recommendations: The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found insufficient evidence to recommend prostate cancer antigen 3 (PCA3) testing to inform decisions for when to rebiopsy previously biopsy-negative patients for prostate cancer or to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (e.g., previous elevated prostate-specific antigen test or suspicious digital rectal examination). The EGAPP Working Group found insufficient evidence to recommend PCA3 testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan. Based on the available evidence, the overall certainty of

clinical validity to predict the diagnosis of prostate cancer using PCA3 is deemed "low." The EGAPP Working Group discourages clinical use for diagnosis unless further evidence supports improved clinical validity. Based on the available evidence, the overall certainty of net health benefit is deemed "low." The EGAPP Working Group discourages clinical use unless further evidence supports improved clinical outcomes. Rationale: It has been suggested that PCA3 testing in the general male population might lead to earlier diagnosis and management changes (e.g., earlier detection and earlier initiation or higher rates of medical interventions) that improve outcomes. EGAPP Working Group found no direct evidence to support this possibility, so we sought indirect evidence aimed at documenting the extent to which PCA3 testing alters prostate cancer diagnosis or management, alone and in combination with traditional clinical management factors, and the extent to which this testing improves health outcomes. Analytic validity: Assay-related evidence was deemed adequate for the PROGENSA PCA3 assay approved by the US Food and Drug Administration, available from Gen-Probe. Very few studies were available that investigated preanalytical effects, analytical performance, and diagnostic accuracy of other quantitative assays for PCA3. Clinical validity: Evidence on clinical validity was rated inadequate to derive any conclusions about performance of PCA3 testing to inform decisions for when to rebiopsy previously biopsy-negative patients for prostate cancer, or to inform decisions to conduct initial biopsies for prostate cancer in at-risk men (e.g., previous elevated prostate-specific antigen test or suspicious digital rectal examination). Furthermore, there was little evidence to derive any conclusions about performance of PCA3 testing in men with cancer-positive biopsies to determine if the disease is indolent or aggressive in order to develop an optimal treatment plan. Clinical utility: No studies were available to provide direct evidence on the balance of benefits and harms related to PCA3 testing for diagnosis and management in the general male population. Evidence for other populations (e.g., high risk) was not evaluated in the review. Contextual issues: Early diagnosis of prostate cancer is central to minimizing morbidity and mortality. Prevention of prostate cancer mortality is a public health priority. Improvements in outcomes associated with PCA3 testing could have important impacts. 

Cameron, M. H., & Huisinga, J. (2014). Objective and subjective measures reflect different aspects of balance in multiple sclerosis. *Journal of Rehabilitation Research and Development, 50*(10), 1401-1410.

The objective of this study was to evaluate relationships between subjective and objective measures of balance in multiple sclerosis (MS). In 54 subjects with MS, balance was measured objectively with the Sensory Organization Test (SOT) using dynamic posturography and subjectively with the Activities-specific Balance Confidence (ABC) Scale and the Falls Efficacy Scale-International (FES-I). MS-related disability was assessed with the Expanded Disability Status Scale (EDSS). Relationships between the magnitude (root mean square, range, and area) as well as velocity of center of pressure sway (calculated from the center of pressure signal from the SOT), composite SOT, ABC Scale, FES-I, and EDSS scores were assessed. The magnitude and velocity of center of pressure sway was statistically significantly correlated with the ABC Scale (rho = -0.2 to -0.5), FES-I (rho = 0.3 to 0.5), and EDSS (rho = 0.3 to 0.4). The composite SOT was also statistically significantly correlated with the ABC Scale, FES-I, and EDSS. Objective balance measures, as reflected by posturography, were significantly related to subjective reports of imbalance and clinical measures of disability in MS. The relationships are moderate to weak, indicating that a comprehensive description of balance problems in people with MS likely requires both objective and subjective balance measures.

Cameron, M. H., Peterson, V., Boudreau, E. A., Downs, A., Lovera, J., Kim, E., et al. (2014). Fatigue is associated with poor sleep in people with multiple sclerosis and cognitive impairment. *Multiple Sclerosis International, 2014*, 872732.

Background. Fatigue is the most common symptom in people with multiple sclerosis (MS). Poor sleep also occurs in this population. Objective. The objective of this study was to determine the relationship between fatigue and sleep quality in people with MS and cognitive impairment. Method. This cross-sectional study assessed relationships among fatigue, assessed with the Modified Fatigue Impact Scale (MFIS) and the Fatigue Severity Scale (FSS), sleep quality assessed with the Pittsburg Sleep Quality Index (PSQI), and demographics in 121 people with MS and cognitive impairment. Results. Fatigue was significantly correlated with poor sleep quality (MFIS: $F = 15.60$, $P < 0.01$; FSS: $F = 12.09$, $P < 0.01$). FSS scores were also significantly

correlated with the PSQI subscore for daytime dysfunction and MFIS scores were significantly correlated with disability, age, and the PSQI subscores for sleep quality, sleep duration, and daytime dysfunction. Conclusions. This study demonstrates a relationship between fatigue and sleep quality in individuals with MS and cognitive impairment.

Carney, P. A., Tucker, E. K., Newby, T. A., & Beer, T. M. (2014). Feasibility, acceptability and findings from a pilot randomized controlled intervention study on the impact of a book designed to inform patients about cancer clinical trials. *Journal of Cancer Education, 29*(1), 181-187.
This study was conducted to assess the feasibility, acceptability, and changes in knowledge among cancer patients assigned to receive a 160-page book on experimental cancer therapies and clinical trials. We enrolled 20 patients with cancer who had never participated in a clinical trial and randomly assigned them to receive the book either during week 1 or week 4 of the study. We collected baseline patient demographic and cancer-related information as well as knowledge about cancer clinical trials at week 0. Follow-up surveys were administered at weeks 3 and 6 for both study groups. Comparisons were made within and between groups randomized to receive the book early (at week 1) to those who received it later (at week 4). One hundred percent of data were captured in both groups at baseline, which decreased to 77.8 % by week 6. The vast majority of participants found the book moderately or very useful (89 % in the Early Group at week 3 and 95.5 % in the Late Group at week 6). Within group pairwise comparisons found significant difference between baseline and week 6 in content-specific knowledge scores among participants in the Late Group [79 % versus 92.1 %, p∈=∈0.01). Global knowledge scores increased significantly for variables reflecting knowledge that promotes decisions to participate in clinical trials. Providing published reading material to patients with cancer is both feasible and acceptable. Offering information to patients about cancer clinical trials, using a book designed for patients with cancer may influence knowledge related to decision to participate in clinical trials. 

Casey, C. M., Bennett, J. A., Winters-Stone, K., Knafl, G. J., & Young, H. M. (2014). Measuring activity levels associated with rehabilitative care in hospitalized older adults. *Geriatric Nursing (New York, N.Y.), 35*(2 Suppl), S3-S10.

Older adults often experience functional losses during hospitalization. Clinical care activities have been increasingly promoted as a way to help older hospitalized patients offset these losses and recover from acute illness. Little research exists to objectively measure clinical care activities. This study evaluated the utility and feasibility of using the Actiheart, a combined heart rate monitor and accelerometer, to measure heart rate and motion (activity counts) during five clinical care activities. Fifty-four adults, aged 65 and older, scheduled for surgery, participated in a simulation of activities. The Actiheart successfully measured motion and heart rate during each of the five activities. One-way repeated measures analyses of variance showed that the Actiheart discriminated significant differences within and across the five activities. This study supports the use of an activity monitor to quantify clinical care activities in research studies that can be translated into clinical care. However, the complexity associated with data collection and analysis using the Actiheart could limit its direct use in clinical research.

Castellano, J. M., Wright, H., Ojeda, S. R., & Lomniczi, A. (2014). An alternative transcription start site yields estrogen unresponsive Kiss1 mRNA transcripts in the hypothalamus of prepubertal female rats. *Neuroendocrinology*,

The importance of the Kiss1 gene in the control of reproductive development is well documented. However, much less is known about the transcriptional regulation of Kiss1 expression in the hypothalamus. Critical for these studies is an accurate identification of the site(s) where Kiss1 transcription is initiated. Employing 5'-RACE PCR we detected a transcription start site (TSS1) used by the hypothalamus of rats, mice, nonhuman primates and humans to initiate Kiss1 transcription. In rodents, an exon 1 encoding 5'-untranslated sequences is followed by an alternatively spliced second exon, which encodes 5'-untranslated regions of two different lengths and contains the translation initiation codon (ATG). In nonhuman primates and humans exon 2 is not alternatively spliced. Surprisingly, in rat mediobasal hypothalamus (MBH), but not preoptic region (POA), an additional TSS (TSS2) located upstream from TSS1 generates an exon 1 longer (377 bp) than the TSS1-derived exon 1 (98 bp). The content of TSS1-derived transcripts increased at puberty in the POA and MBH of female rats. It also increased in the MBH after ovariectomy, and this change was prevented by estrogen. In contrast, no such changes in TSS2-derived transcript abundance were detected. Promoter assays showed that the proximal TSS1

promoter is much more active than the putative TSS2 promoter, and that only the TSS1 promoter is regulated by estrogen. These differences appear to be related to the presence of a TATA box and binding sites for transcription factors activating transcription and interacting with estrogen receptor alpha (ERalpha) in the TSS1, but not TSS2, promoter. (c) 2014 S. Karger AG, Basel.

Caughey, A. (2014). Induction of labour: Does it increase the risk of cesarean delivery? *BJOG : An International Journal of Obstetrics and Gynaecology*, *121*(6), 658-661.

Centeno, C. J., & Freeman, M. D. (2014). Percutaneous injection of autologous, culture-expanded mesenchymal stem cells into carpometacarpal hand joints: A case series with an untreated comparison group. *Wiener Medizinische Wochenschrift*, *164*(5-6), 83-87.
In the present study, we describe six patients who received autologous mesenchymal stem cell (MSC) therapy for symptomatic carpometacarpal (CMC) joint and hand osteoarthritis (OA). Six patients who received injections of adult autologous culture expanded MSCs in their thumb CMC joints were followed for 1 year posttreatment, and matched with four procedure candidates who remained untreated. We observed positive outcomes in the treatment group for both symptoms and function related to the OA, compared with a reported worsening among the untreated controls. While these results should be interpreted with caution because of the small number of treated subjects and lack of placebo control and randomization, we find sufficient evidence for further investigation of MSC therapy as an alternative to more invasive surgery in patients with OA of the hand. © 2013 Springer-Verlag.

Chang, H., Zhou, Y., Spellman, P., & Parvin, B. (2013). Stacked predictive sparse coding for classification of distinct regions in tumor histopathology. *2013 14th IEEE International Conference on Computer Vision*, *ICCV 2013*, Sydney, NSW. pp. 169-176.
Image-based classification of histology sections, in terms of distinct components (e.g., tumor, stroma, normal), provides a series of indices for tumor composition. Furthermore, aggregation of these indices, from each whole slide image (WSI) in a large cohort, can provide predictive models of the clinical outcome. However, performance of the existing techniques is hindered as a result of large technical variations and biological heterogeneities that are always present in a large

cohort. We propose a system that automatically learns a series of basis functions for representing the underlying spatial distribution using stacked predictive sparse decomposition (PSD). The learned representation is then fed into the spatial pyramid matching framework (SPM) with a linear SVM classifier. The system has been evaluated for classification of (a) distinct histological components for two cohorts of tumor types, and (b) colony organization of normal and malignant cell lines in 3D cell culture models. Throughput has been increased through the utility of graphical processing unit (GPU), and evaluation indicates a superior performance results, compared with previous research. © 2013 IEEE.

Ching, A. C. (2014). How do we interpret national inpatient sample data about complications?: Commentary on an article by amit jain, MD, et al.: "rhBMP use in cervical spine surgery: Associated factors and in-hospital complications". *The Journal of Bone and Joint Surgery.American Volume*, *96*(8), e67.

Chiu, D. T., Shapiro, N. I., Sun, B. C., Mottley, J. L., & Grossman, S. A. (2014). Are echocardiography, telemetry, ambulatory electrocardiography monitoring, and cardiac enzymes in emergency department patients presenting with syncope useful tests? A preliminary investigation. *The Journal of Emergency Medicine*,

BACKGROUND: Prior studies of admitted geriatric syncope patients suggest that diagnostic tests affect management /= 18 years presenting with syncope was conducted. The four most commonly utilized tests (echocardiography, telemetry, ambulatory electrocardiography monitoring, and troponin) were studied. Interobserver agreement as to whether test results determined the etiology of the syncope was measured using kappa (kappa) values. RESULTS: Of 570 patients with syncope, 73 patients (8%; 95% confidence interval 7-10%) had studies that were diagnostic. One hundred fifty (26%) had echocardiography, with 33 (22%) demonstrating a likely etiology of the syncopal event, such as critical valvular disease or significantly depressed left ventricular function (kappa = 0.75). On hospitalization, 330 (58%) patients were placed on telemetry, and 19 (3%) had worrisome dysrhythmias (kappa = 0.66). There were 317 (55%) patients who had troponin levels drawn, of whom 19 (3%) had positive results (kappa = 1); 56 (10%) patients were discharged with monitoring, with significant findings in only 2 (0.4%)

patients (kappa = 0.65). CONCLUSION: Although routine testing is prevalent in ED patients with syncope, the diagnostic yield is relatively low. Nevertheless, some testing, particularly echocardiography, may yield critical findings. Current efforts to reduce the cost of medical care by eliminating nondiagnostic medical testing and increasing emphasis on practicing evidence-based medicine argue for more discriminate testing when evaluating syncope.

Choi, M., Holliday, E. B., Jagsi, R., Wilson, L. D., Fuller, C. D., & Thomas, C. R.,Jr. (2014). Citation-based estimation of scholarly activity among domestic academic radiation oncologists: Five-year update. *Journal of Radiation Oncology*, *3*(1), 115-122.

OBJECTIVE: To analyze up-to-date Hirsch index (h-index) data to estimate the scholarly productivity of academic radiation oncology faculty. METHODS: Bibliometric citation database searches were performed for radiation oncology faculty at domestic residency-training institutions. Outcomes analyzed included the number of manuscripts, number of citations, and h-index between 1996 and 2012. Analyses of overall h-index rankings with stratification by academic ranking, gender, and departmental faculty size were performed. RESULTS: One thousand thirty-seven radiation oncologists from 87 programs were included. Overall, the mean h-index was 10.8. Among the top 10% by h-index, 38% were chairpersons, all were senior faculty, and 11% were women. As expected, higher h-index was associated with higher academic ranking and senior faculty status. Recursive partitioning analysis revealed an h-index threshold of 20 ($p < 0.001$) as an identified breakpoint between senior vs. junior faculty. Furthermore, h-index breakpoints of 12 ($p < 0.001$) and 25 ($p < 0.001$) were identified between assistant professor vs. associate professor, and associate professor vs. professor levels, respectively. Multivariate analysis identified higher academic ranking, male gender, and larger departmental faculty size as independent variables associated with higher h-index. CONCLUSION: The current results suggest an overall rise in scholarly citation metrics among domestic academic radiation oncologists, with a current mean h-index of 10.8, vs. 8.5 in 2008. Significant relationships exist between h-index and academic rank, gender, and departmental size. The results offer up-to-date benchmarks for evaluating academic radiation oncologist to the national average and potentially has utility in the process of appointment and promotion decisions.

Cholerton, B. A., Zabetian, C. P., Wan, J. Y., Montine, T. J., Quinn, J. F., Mata, I. F., et al. (2014). Evaluation of mild cognitive impairment subtypes in parkinson's disease. *Movement Disorders*,

Mild cognitive impairment in Parkinson's disease (PD-MCI) is common and increases the risk for dementia. Establishing distinct PD-MCI cognitive subtypes could be valuable for eventually predicting those most likely to convert to dementia. However, the study of PD-MCI subtypes has not yielded consistent results among cohorts. To determine whether there are distinct cognitive subtypes among participants diagnosed with PD-MCI in the Pacific Northwest Udall Center Clinical Consortium, we cognitively subtyped 95 patients with PD-MCI, using the Movement Disorders Society Task Force diagnostic guidelines. Psychometric test scores were then subjected to principle components factor analysis to determine whether similar cognitive subgroups could be identified using statistical methodology. Multiple-domain PD-MCI was diagnosed in 95% of the sample, and a range of cognitive impairments were noted. Factor analysis yielded seven factors and demonstrated overlap of phonemic verbal fluency on two factors, as well as the loading of verbal fluency on the same factor as a visuospatial measure; however, these factors did not partition the sample into distinct cognitive subtypes. Separation of cognitive subtypes based on the current PD-MCI criteria, or via statistical methods, may not provide sufficient information to describe distinct PD groups. Future efforts to validate the PD-MCI criteria and identify combinations of genetic or other risk factors for cognitive impairment are warranted. © 2014 International Parkinson and Movement Disorder Society.

Choo, E. K., Benz, M., Zaller, N., Warren, O., Rising, K. L., & McConnell, K. J. (2014). The impact of state medical marijuana legislation on adolescent marijuana use. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*,

PURPOSE: The state-level legalization of medical marijuana has raised concerns about increased accessibility and appeal of the drug to youth. The objective of this study was to assess the impact of medical marijuana legalization across the United States by comparing trends in adolescent marijuana use between states with and without legalization of medical marijuana. METHODS: The study utilized data from the Youth Risk Behavioral Surveillance Survey between 1991 and 2011. States with a medical marijuana law for which at least two cycles of Youth Risk Behavioral Surveillance data were available before and after the implementation of the law were selected for

analysis. Each of these states was paired with a state in geographic proximity that had not implemented the law. Chi-squared analysis was used to compare characteristics between states with and without medical marijuana use policies. A difference-in-difference regression was performed to control for time-invariant factors relating to drug use in each state, isolating the policy effect, and then calculated the marginal probabilities of policy change on the binary dependent variable. RESULTS: The estimation sample was 11,703,100 students. Across years and states, past-month marijuana use was common (20.9%, 95% confidence interval 20.3-21.4). There were no statistically significant differences in marijuana use before and after policy change for any state pairing. In the regression analysis, we did not find an overall increased probability of marijuana use related to the policy change (marginal probability .007, 95% confidence interval -.007, .02). CONCLUSIONS: This study did not find increases in adolescent marijuana use related to legalization of medical marijuana.

Chou, R., Cruciani, R. A., Fiellin, D. A., Compton, P., Farrar, J. T., Haigney, M. C., et al. (2014). Methadone safety: A clinical practice guideline from the american pain society and college on problems of drug dependence, in collaboration with the heart rhythm society. *The Journal of Pain : Official Journal of the American Pain Society*, *15*(4), 321-337.

Methadone is used for the treatment of opioid addiction and for treatment of chronic pain. The safety of methadone has been called into question by data indicating a large increase in the number of methadone-associated overdose deaths in recent years that has occurred in parallel with a dramatic rise in the use of methadone for chronic pain. The American Pain Society and the College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society, commissioned an interdisciplinary expert panel to develop a clinical practice guideline on safer prescribing of methadone for treatment of opioid addiction and chronic pain. As part of the guideline development process, the American Pain Society commissioned a systematic review of various aspects related to safety of methadone. After a review of the available evidence, the expert panel concluded that measures can be taken to promote safer use of methadone. Specific recommendations include the need to educate and counsel patients on methadone safety, use of electrocardiography to identify persons at greater risk for methadone-associated arrhythmia, use of alternative opioids in patients at high risk of complications related to corrected

electrocardiographic QTc interval prolongation, careful dose initiation and titration of methadone, and diligent monitoring and follow-up. Although these guidelines are based on a systematic review, the panel identified numerous research gaps, most recommendations were based on low-quality evidence, and no recommendations were based on high-quality evidence. PERSPECTIVE: This guideline, based on a systematic review of the evidence on methadone safety, provides recommendations developed by a multidisciplinary expert panel. Safe use of methadone requires clinical skills and knowledge in use of methadone to mitigate potential risks, including serious risks related to risk of overdose and cardiac arrhythmias.

Chou, R., Weimer, M. B., & Dana, T. (2014). Methadone overdose and cardiac arrhythmia potential: Findings from a review of the evidence for an american pain society and college on problems of drug dependence clinical practice guideline. *The Journal of Pain : Official Journal of the American Pain Society, 15*(4), 338-365.

The number of deaths associated with methadone use increased dramatically in parallel with marked increases in its use, particularly for treatment of chronic pain. To develop a clinical guideline on methadone prescribing to reduce potential harms, the American Pain Society commissioned a review of various aspects related to methadone safety. This article summarizes evidence related to unintentional overdose due to methadone and harms related to cardiac arrhythmia potential. We searched Ovid MEDLINE, the Cochrane Library, and PsycINFO databases through January 2014 for studies assessing harms associated with methadone use; we judged 70 studies to be relevant and to meet inclusion criteria. The majority of studies on overdose and cardiac arrhythmia risk are observational and provide weak evidence on which to base clinical guidelines. In patients prescribed methadone for treatment of opioid dependence, data suggest that mortality benefits related to reduction in illicit drug use outweigh harms. Despite epidemiologic data showing marked increases in the numbers of methadone-related deaths that have been primarily attributed to increased use of methadone for chronic pain, evidence on methadone and mortality risk in this population has been somewhat contradictory. There is some evidence that recent initiation of methadone, psychiatric admissions, and concomitant use of benzodiazepines are associated with a higher risk for overdose. Evidence on cardiac risks is primarily limited to case reports of torsades de pointes, primarily in patients on high doses of

methadone, and to studies showing an association between methadone use and prolongation of QTc intervals. Research is needed to understand the effectiveness of dosing methods, electrocardiogram monitoring, and other risk mitigation strategies in patients prescribed methadone. PERSPECTIVE: This systematic review synthesizes the evidence related to methadone use and risk for overdose and cardiac arrhythmia. Findings regarding the association between methadone use and QTc interval prolongation and risk factors for methadone-associated overdose suggest potential targets for risk mitigation strategies, though research is needed to determine the effectiveness of such strategies at reducing adverse outcomes.

Chou, S., Boivin, G., Ives, J., & Elston, R. (2014). Phenotypic evaluation of previously uncharacterized cytomegalovirus DNA polymerase sequence variants detected in a valganciclovir treatment trial. *Journal of Infectious Diseases, 209*(8), 1219-1226.

Background. In a large randomized trial comparing oral valganciclovir and intravenous ganciclovir for treatment of cytomegalovirus disease in solid organ transplantation, confirmed genotypic drug resistance was uncommon (20 sequence variants, including the nonviable mutations and several resistance mutations.Conclusions. Newly phenotyped UL54 sequence variants did not significantly change the reported incidence of drug resistance in the clinical trial. Unrecognized sequence variants in diagnostic genotyping reports should be confirmed by additional testing in order to improve clinical decision making. © 2013 The Author 2013.

Clark, K. M., Yu, Y., van der Donk, W. A., Blackburn, N., & Lu, Y. (2014). Modulating the copper-sulfur interaction in type 1 blue copper azurin by replacing Cys112 with nonproteinogenic homocysteine. *Inorganic Chemistry Frontiers, 1*(2), 153-158.

The Cu-SCys interaction is known to play a dominant role in defining the type 1 (T1) blue copper center with respect to both its electronic structure and electron transfer function. Despite this importance, its role has yet to be probed by mutagenesis studies without dramatic change of its T1 copper character. We herein report replacement of the conserved Cys112 in azurin with the nonproteinogenic amino acid homocysteine. Based on electronic absorption, electron paramagnetic resonance, and extended x-ray absorption fine structural spectroscopic studies, this variant displays typical type 1 copper site features. Surprisingly, instead of increasing the

strength of the Cu-sulfur interaction by the introduction of the extra methylene group, the Cys112Hcy azurin showed a decrease in the covalent interaction between SHcy and Cu(II) when compared with the WT SCys-Cu(II) interaction. This is likely due to geometric adjustment of the center that resulted in the copper ion moving out of the trigonal plane defined by two histidines and one Hcy and closer to Met121. These structural changes resulted in an increase of reduction potential by 35 mV, consistent with lower Cu-S covalency. These results suggest that the Cu-SCys interaction is close to being optimal in native blue copper protein. It also demonstrates the power of using nonproteinogenic amino acids in addressing important issues in bioinorganic chemistry.

Collister, J. P., Nahey, D. B., Hendel, M. D., & Brooks, V. L. (2014). Roles of the subfornical organ and area postrema in arterial pressure increases induced by 48-h water deprivation in normal rats. *Physiological Reports, 2*(1), e00191.

In rats, water deprivation (WD) increases arterial blood pressure (BP) in part due to actions of elevated osmolality in the brain to increase vasopressin levels and sympathetic activity. However, the osmoreceptors that mediate this response have not been identified. To test the hypothesis that osmoregulatory circumventricular organs are involved, BP and heart rate (HR) were continuously recorded telemetrically during 48 h of WD in normal rats with lesions (x) or sham lesions (sham) of the subfornical organ (SFO) or area postrema (AP). Although WD increased BP in SFOx and SFOsham rats, no significant difference in the hypertensive response was observed between groups. HR decreased transiently but similarly in SFOx and SFOsham rats during the first 24 h of WD. When water was reintroduced, BP and HR decreased rapidly and similarly in both groups. BP (during lights off) and HR were both lower in APx rats before WD compared to APsham. WD increased BP less in APx rats, and the transient bradycardia was eliminated. Upon reintroduction of drinking water, smaller falls in both BP and HR were observed in APx rats compared to APsham rats. WD increased plasma osmolality and vasopressin levels similarly in APx and APsham rats, and acute blockade of systemic V1 vasopressin receptors elicited similar depressor responses, suggesting that the attenuated BP response is not due to smaller increases in vasopressin or osmolality. In conclusion, the AP, but not the SFO, is required for the maximal hypertensive effect induced by WD in rats.

Coronado, G. D., Sanchez, J., Petrik, A., Kapka, T., Devoe, J., & Green, B. (2014). Advantages of wordless instructions on how to complete a fecal immunochemical test: Lessons from patient advisory council members of a federally qualified health center. *Journal of Cancer Education, 29*(1), 86-90.

Some patients face difficulty understanding instructions for completing the fecal immunochemical test (FIT), a self-administered test to screen for colorectal cancer. We sought to develop and test low-literacy instructions for completing the FIT. Working in partnership with a Latino-serving Federally Qualified Health Center (FQHC) in the Portland Metro area, we developed and tested low-literacy instructions for completing the FIT; the instructions contained seven words (mail within 3 days; Devolver dentro de 3 dias). We conducted focus groups of Spanish-speaking patients on the advisory council of our partnering FQHC organization, and we gathered feedback from the project's advisory board members and clinic staff. We mailed a FIT kit to each patient, along with either (a) instructions written in English and Spanish, consisting of 415 words; or (b) low-literacy "wordless" instructions. We asked patients to complete the test before providing feedback. Our qualitative assessment showed that the wordless instructions were preferred over instructions consisting of words. Wordless instructions might aid efforts to raise the rates of colorectal cancer screening among low-literacy and non-English-speaking populations. © 2013 Springer Science+Business Media New York.

Creeley, C. E., Dikranian, K. T., Dissen, G. A., Back, S. A., Olney, J. W., & Brambrink, A. M. (2014). Isoflurane-induced apoptosis of neurons and oligodendrocytes in the fetal rhesus macaque brain. *Anesthesiology, 120*(3), 626-638.

BACKGROUND: The authors have previously shown that exposure of the neonatal nonhuman primate (NHP) brain to isoflurane for 5 h causes widespread acute apoptotic degeneration of neurons and oligodendrocyte. The current study explored the potential apoptogenic action of isoflurane in the fetal NHP brain. METHODS: Fetal rhesus macaques at gestational age of 120 days (G120) were exposed in utero for 5 h to isoflurane anesthesia (n = 5) or to no anesthesia (control condition; n = 4), and all regions of the brain were systematically evaluated 3 h later for evidence of apoptotic degeneration of neurons or glia. RESULTS: Exposure of the G120 fetal NHP brain to isoflurane caused a significant increase in apoptosis of neurons and of oligodendrocytes

at a stage when oligodendrocytes were just beginning to myelinate axons. The neuroapoptosis response was most prominent in the cerebellum, caudate, putamen, amygdala, and several cerebrocortical regions. Oligodendrocyte apoptosis was diffusely distributed over many white matter regions. The total number of apoptotic profiles (neurons + oligodendrocytes) in the isoflurane-exposed brains was increased 4.1-fold, compared with the brains from drug-naive controls. The total number of oligodendrocytes deleted by isoflurane was higher than the number of neurons deleted. CONCLUSIONS: Isoflurane anesthesia for 5 h causes death of neurons and oligodendrocytes in the G120 fetal NHP brain. In the fetal brain, as the authors previously found in the neonatal NHP brain, oligodendrocytes become vulnerable when they are just achieving myelination competence. The neurotoxic potential of isoflurane increases between the third trimester (G120) and the neonatal period in the NHP brain.

Cunha-Cruz, J., Pashova, H., Packard, J. D., Zhou, L., Hilton, T. J., & for Northwest PRECEDENT. (2010). Tooth wear: Prevalence and associated factors in general practice patients. *Community Dentistry and Oral Epidemiology*, *38*(3), 228-234.

OBJECTIVES: To estimate the prevalence of tooth wear and to investigate factors associated with tooth wear in patients from general practices in the Northwest United States. METHODS: Data on the diagnosis and treatment of oral diseases during the previous year were collected in a survey with a systematic random sample of patients (n= 1530) visiting general dentists from the Northwest Practice-based REsearch Collaborative in Evidence-based DENTistry (PRECEDENT) (n=80). Prevalence ratios (PRs) of moderate to severe occlusal and incisal tooth wear by patient characteristics were estimated using cluster-adjusted multiple binomial regression for adults (18+ years) and children/adolescents (3-17 years). RESULTS: For adults, the mean number of teeth with wear facets was 5.4 [95% confidence interval (CI) =4.6-6.2] and 51% of the adults had four or more teeth with wear. Participants 45-64 and 65+ years old were 1.3 (95% CI=1.1-1.6) and 1.4 (95% CI=1.1-1.8) times as likely to have 4+ teeth with moderate to severe wear facets as participants 18-44 years old. Adult males had a 20% (PR=1.2; 95% CI=1.1-1.4) higher prevalence of wear than adult females. Adults who were using, or had ever used occlusal splints had higher prevalence of tooth wear compared to those who never used such appliances (PR=1.3; 95% CI=1.0-1.5). Adults with any periodontal bone loss also had a 20% higher

prevalence of wear than adults without periodontal disease (PR=1.2; 95% CI=1.0-1.4). For children/adolescents, the mean number of teeth with moderate to severe wear facets was 1.6 (95% CI=0.9-2.6) and 31% of the children had one or more teeth with wear facets. The adjusted prevalence ratio of tooth wear (1+ teeth with wear facets) for boys was 1.6 times as high (95% CI=1.1-2.4) as compared with girls. The prevalence of wear for children 12+ years old was 50% (PR=0.5; 95% CI=0.3-0.8) lower than that of children <12 years old. Angle's class II was associated with higher tooth wear prevalence (PR= 1.8; 95% CI=1.3-2.6) than class I. Children with posterior or anterior open bite had lower prevalence of wear than their counterparts (PR=0.6; 95% CI=0.3-1.0). No associations were observed between tooth wear and orthodontic treatment, missing teeth, and race/ethnicity. CONCLUSION: Tooth wear is a prevalent condition in this population. Among adults, higher prevalences of tooth wear were observed among those who were older, males, had used occlusal splints and had periodontal disease. Among children, higher prevalences were associated with younger age, male gender, class II malocclusion and the absence of open bite. Submitted on behalf of the Northwest PRECEDENT network, with support from NIDCR grants DE016750 and DE016752.

Curry, M., Whitney, N., Roundy, N., & Selden, N. R. (2014). A case of acute traumatic subdural hematoma in a child with previous bilateral encephaloduroarteriosynangiosis. *Child's Nervous System*, *30*(4), 699-702.

The authors report the case of a 5-year-old female with right-sided hemiparesis and aphasia secondary to moyamoya disease, who had previously undergone staged bilateral encephaloduroarteriosynangiosis procedures. A subsequent ground-level fall caused an acute traumatic subdural hematoma with mass effect and neurological decline. She underwent emergency hematoma evacuation and decompressive craniectomy, which required interruption of the superficial temporal artery that had been used for indirect bypass, followed later by autologous cranioplasty. There were no acute or long-term ischemic events related to the occurrence or treatment of the traumatic hematoma. Follow-up angiography revealed extensive spontaneous vascular collateralization in the field of the decompressive craniectomy and cranioplasty. The patient returned to her pre-injury neurological baseline. 

Davis, M. M., Freeman, M., Kaye, J., Vuckovic, N., & Buckley, D. I. (2014). A systematic review of clinician and staff views on the acceptability of incorporating remote monitoring technology into primary care. *Telemedicine Journal and e-Health : The Official Journal of the American Telemedicine Association*,

Abstract Objective: Remote monitoring technology (RMT) may enhance healthcare quality and reduce costs. RMT adoption depends on perceptions of the end-user (e.g., patients, caregivers, healthcare providers). We conducted a systematic review exploring the acceptability and feasibility of RMT use in routine adult patient care, from the perspectives of primary care clinicians, administrators, and clinic staff. Materials and Methods: We searched the databases of Medline, IEEE Xplore, and Compendex for original articles published from January 1996 through February 2013. We manually screened bibliographies of pertinent studies and consulted experts to identify English-language studies meeting our inclusion criteria. Results: Of 939 citations identified, 15 studies reported in 16 publications met inclusion criteria. Studies were heterogeneous by country, type of RMT used, patient and provider characteristics, and method of implementation and evaluation. Clinicians, staff, and administrators generally held positive views about RMTs. Concerns emerged regarding clinical relevance of RMT data, changing clinical roles and patterns of care (e.g., reduced quality of care from fewer patient visits, overtreatment), insufficient staffing or time to monitor and discuss RMT data, data incompatibility with a clinic's electronic health record (EHR), and unclear legal liability regarding response protocols. Conclusions: This small body of heterogeneous literature suggests that for RMTs to be adopted in primary care, researchers and developers must ensure clinical relevance, support adequate infrastructure, streamline data transmission into EHR systems, attend to changing care patterns and professional roles, and clarify response protocols. There is a critical need to engage end-users in the development and implementation of RMT.

Denneson, L. M., Corson, K., Helmer, D. A., Bair, M. J., & Dobscha, S. K. (2014). Mental health utilization of new-to-care iraq and afghanistan veterans following suicidal ideation assessment. *Psychiatry Research*,

We evaluated the impact of brief structured suicidal ideation (SI) assessments on mental health care among new-to-care Operations Enduring Freedom and Iraqi Freedom (OEF/OIF) veterans.

National datasets provided military, demographic, and clinical information. For all new-to-care OEF/OIF veterans administered depression screens (PHQ-2: Patient Health Questionnaire-2) and structured SI assessments in primary care or ambulatory mental health settings of three Veterans Affairs (VA) Medical Centers between April 2008 and September 2009 (N=465), generalized estimating equations were used to examine associations between SI and number of subsequent-year specialty mental health visits and antidepressant prescriptions. Approximately one-third of the veterans reported SI. In multivariate models, PTSD and anxiety diagnoses, severe depression symptoms, being married, and SI assessment by a mental health clinician were associated with more mental health visits in the subsequent year. Depression, PTSD, and anxiety diagnoses, and SI assessment by a mental health clinician were associated with receiving antidepressants. Presence of SI did not significantly affect subsequent year mental health utilization when adjusting for diagnostic and clinician variables, but inaugural visits involving mental health clinicians were consistently associated with subsequent mental health care.

Doss, A., & Pereira, L. (2014). Strip of the month: April 2014. *Neoreviews, 15*(4), e155-e162.

D'Souza, S. L., Elmunzer, B. J., & Scheiman, J. M. (2014). Long-term follow-up of asymptomatic pancreatic neuroendocrine tumors in multiple endocrine neoplasia type i syndrome. *Journal of Clinical Gastroenterology, 48*(5), 458-461.

Background and Aims: Pancreatic neuroendocrine tumors (PNETs) in asymptomatic patients may contribute to mortality. Endoscopic ultrasound (EUS) is the most accurate test to identify and monitor tumor size. The aim of this study was to examine the rate of growth and development of new tumors in multiple endocrine neoplasia type I (MEN 1). Materials and Methods: A retrospective cohort study in a tertiary academic center. Patients identified in endoscopic databases were included if they had 2 or more EUS examinations with untreated asymptomatic tumors identified. The growth rate and incidence of new lesions was analyzed. Results: A total of 11 patients were studied (7 female, 4 male). Initially, 18 lesions with an average size of 10.3 mm (range, 5 to 24 mm) were found. Mean surveillance was 79 months (range, 18 to 134 mo). The growth rate of index lesions was 1.32 mm/y; 11 lesions exhibited stability or a decrease in size. Twelve new lesions were identified in 7 patients during the surveillance period with an average

growth rate of 3.0 mm/y. The earliest new lesion was identified at 12 months and the latest at 70 months after index EUS. New lesions had a faster growth rate than those seen on initial EUS (P=0.01). Conclusions: Multiple endocrine neoplasia type I patients exhibit an overall low rate of growth of pancreatic neuroendocrine tumors. Growth rate of newly diagnosed lesions was significantly faster, suggesting a variation in phenotypic expression of the disease. Therapy should be individualized based upon the tumor size and location, symptoms, overall clinical status, and operative risk. © 2013 Lippincott Williams & Wilkins.

Eiff, M. P., Garvin, R., Green, L. A., Pugno, P. A., Kozakowski, S., Dostal, J., et al. (2014). Innovating within the ACGME regulatory environment is not an oxymoron. *Family Medicine*, *46*(4), 282-287. BACKGROUND AND OBJECTIVES: The aim of this study was to describe the analysis of program citations and cycle length for reaccreditation in the 14 family medicine residencies participating in the P4 project. METHODS: An exploratory narrative analysis was conducted on all actions taken by the Review Committee for Family Medicine (RCFM) between 2003 and 2012. The analysis included cycle length and types of citations associated with accreditation actions. Several validation steps were undertaken to confirm findings reported. RESULTS: Mean cycle length for all P4 programs was 4.0 before P4 (2007) and did not change significantly during P4. The average number of citations per program before P4 was 6.2, and during P4 the average was 6.8. The P4 averages were similar to national norms during the project period. The citations that most commonly decreased during the P4 project were: Continuity of Patient Care/ Inpatient, FMC Patient Population/Patient Volume, Orthopedics or Sports Medicine Curriculum, Resident Final Evaluation, Resident Workload/Duty Hours, and Resident Attrition. The citations that most commonly increased during the P4 project were FMC Patient Population/Demographics, Certifying Exam Scores, and Management of Health Systems Curriculum. CONCLUSIONS: Innovation and redesign of residency training in the P4 programs appears not to have affected the average cycle length or number of citations per program. The current regulatory environment in family medicine residency education appears to allow for innovation and experimentation.

Elbarbry, F., Vermehren-Schmaedick, A., & Balkowiec, A. (2014). Modulation of arachidonic acid metabolism in the rat kidney by sulforaphane: Implications for regulation of blood pressure. *ISRN*

*Pharmacology, 2014*, 683508.

Background. We investigated the effects of sulforaphane (SF), the main active isothiocyanate in cruciferous vegetables, on arachidonic acid (AA) metabolism in the kidney and its effect on arterial blood pressure, using spontaneously hypertensive rats (SHR) as models. Methods. Rats were treated for 8 weeks with either drinking water alone (control) or SF (20 or 40 mg/kg) added to drinking water. Mean arterial pressure (MAP) was measured at 7-day intervals throughout the study. At the end of treatment rats were euthanized, and kidneys were harvested to prepare microsomes and measure enzymes involved in regulation of vasoactive metabolites: CYP4A, the key enzyme in the formation of 20-hydroxyeicosatetraenoic acid, and the soluble epoxide hydrolase, which is responsible for the degradation of the vasodilator metabolites such as epoxyeicosatetraenoic acids. Effect of SF on kidney expression of CYP4A was investigated by immunoblotting. Results. We found that treatment with SF leads to significant reductions in both, the expression and activity of renal CYP4A isozymes, as well as the activity of soluble epoxide hydrolase (sEH). Consistent with these data, we have found that treatment with SF resisted the progressive rise in MAP in the developing SHR in a dose-dependent manner. Conclusion. This is the first demonstration that SF modulates the metabolism of AA by both P450 enzymes and sEH in SHR rats. This may represent a novel mechanism by which SF protects SHR rats against the progressive rise in blood pressure.

Enninga, E. A., Holtan, S. G., Creedon, D. J., Dronca, R. S., Nevala, W. K., Ognjanovic, S., et al. (2014). Immunomodulatory effects of sex hormones: Requirements for pregnancy and relevance in melanoma. *Mayo Clinic Proceedings, 89*(4), 520-535.

Similarities between the pathologic progression of cancer and the physiologic process of placentation (eg, proliferation, invasion, and local/systemic tolerance) have been recognized for many years. Sex hormones such as human chorionic gonadotropin, estrogens, progesterone, and others contribute to induction of immunologic tolerance at the beginning of gestation. Sex hormones have been shown to play contributory roles in the growth of cancers such as breast cancer, prostrate cancer, endometrial cancer, and ovarian cancer, but their involvement as putative mediators of the immunologic escape of cancer is still being elucidated. Herein, we compare the emerging mechanism by which sex hormones modulate systemic immunity in

pregnancy and their potentially similar role in cancer. To do this, we conducted a PubMed search using combinations of the following keywords: "immune regulation," "sex hormones," "pregnancy," "melanoma," and "cancer." We did not limit our search to specific publication dates. Mimicking the maternal immune response to pregnancy, especially in late gestation, might aid in design of better therapies to reconstitute endogenous antitumor immunity and improve survival.

Ensrud, K. E., Parimi, N., Fink, H. A., Ishani, A., Taylor, B. C., Steffes, M., et al. (2014). Estimated GFR and risk of hip fracture in older men: Comparison of associations using cystatin C and creatinine. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation, 63*(1), 31-39.

BACKGROUND: Higher serum cystatin C level is associated with an increased risk of hip fracture in postmenopausal white women, but there is a paucity of data for men. Whether estimated glomerular filtration rate (eGFR) based on cystatin C (eGFRcys) is superior in predicting hip fracture risk to eGFR based on creatinine (eGFRcr) or the combination (eGFR(cr-cys)) also is uncertain. STUDY DESIGN: Nested case-cohort. SETTING & PARTICIPANTS: Participants enrolled in the Osteoporotic Fractures in Men (MrOS) Study (5,994 men aged >/= 65 years from 6 US centers) including a random subcohort of 1,602 men and 168 men with incident hip fractures (51 of whom were in the subcohort). PREDICTOR: eGFR(cys), eGFR(cr), and eGFR(cr-cys) computed using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations and expressed in categories of /= 75 mL/min/1.73 m(2) (referent group). OUTCOME: Incident hip fracture ascertained by participant contacts every 4 months and confirmed with radiographic reports. RESULTS: Median eGFR(cys) was 72.9 (IQR, 60.5-85.7) mL/min/1.73 m(2). In unadjusted models, all measures of eGFR were associated with increased hip fracture risk. However, after adjustment for age, race, site, and body mass index, the association of lower eGFR(cys) (but not lower eGFR(cr) or lower eGFR(cr-cys)) with higher hip fracture risk remained: for /= 75 mL/min/1.73 m(2), HRs were 1.96 [95% CI, 1.25-3.09], 0.84 [95% CI, 0.52-1.37], and 1.08 [95% CI, 0.66-1.77] for eGFR(cys), eGFR(cr), and eGFR(cr-cys), respectively. Similarly, after adjustment for age, race, site, and body mass index, eGFR /= 75 mL/min/1.73 m(2), HRs were 1.96 [95% CI, 1.25-3.09], 0.84 [95% CI, 0.52-1.37], and 1.08 [95% CI, 0.66-1.77] for eGFR(cys), eGFR(cr), and eGFR(cr-cys), respectively. Similarly, after adjustment for age, race,

site, and body mass index, eGFR /= 75 mL/min/1.73 m(2): HR, 1.43; 95% CI, 0.88-2.34) after consideration of additional clinical risk factors and bone mineral density. LIMITATIONS: Findings not generalizable to other populations; residual confounding may exist. CONCLUSIONS: Older community-dwelling men with lower eGFR(cys) have an increased risk of hip fracture that is explained in large part by greater burden of risk factors among men with lower eGFR(cys). In contrast, lower eGFR(cr) or lower eGFR(cr-cys) was not associated with a higher age-adjusted hip fracture risk.

Espey, D. K., Jim, M. A., Cobb, N., Bartholomew, M., Becker, T., Haverkamp, D., et al. (2014). Leading causes of death and all-cause mortality in american indians and alaska natives. *American Journal of Public Health*,

Objectives. We present regional patterns and trends in all-cause mortality and leading causes of death in American Indians and Alaska Natives (AI/ANs). Methods. US National Death Index records were linked with Indian Health Service (IHS) registration records to identify AI/AN deaths misclassified as non-AI/AN. We analyzed temporal trends for 1990 to 2009 and comparisons between non-Hispanic AI/AN and non-Hispanic White persons by geographic region for 1999 to 2009. Results focus on IHS Contract Health Service Delivery Area counties in which less race misclassification occurs. Results. From 1990 to 2009 AI/AN persons did not experience the significant decreases in all-cause mortality seen for Whites. For 1999 to 2009 the all-cause death rate in CHSDA counties for AI/AN persons was 46% more than that for Whites. Death rates for AI/AN persons varied as much as 50% among regions. Except for heart disease and cancer, subsequent ranking of specific causes of death differed considerably between AI/AN and White persons. Conclusions. AI/AN populations continue to experience much higher death rates than Whites. Patterns of mortality are strongly influenced by the high incidence of diabetes, smoking prevalence, problem drinking, and social determinants. Much of the observed excess mortality can be addressed through known public health interventions. (Am J Public Health. Published online ahead of print April 22, 2014: e1-e9. doi:10.2105/AJPH.2013.301798).

Facchinetti, A., Del Favero, S., Sparacino, G., Castle, J. R., Ward, W. K., & Cobelli, C. (2014). Modeling the glucose sensor error. *IEEE Transactions on Biomedical Engineering*, *61*(3), 620-629.

Continuous glucose monitoring (CGM) sensors are portable devices, employed in the treatment of diabetes, able to measure glucose concentration in the interstitium almost continuously for several days. However, CGM sensors are not as accurate as standard blood glucose (BG) meters. Studies comparing CGM versus BG demonstrated that CGM is affected by distortion due to diffusion processes and by time-varying systematic under/overestimations due to calibrations and sensor drifts. In addition, measurement noise is also present in CGM data. A reliable model of the different components of CGM inaccuracy with respect to BG (briefly, "sensor error") is important in several applications, e.g., design of optimal digital filters for denoising of CGM data, real-time glucose prediction, insulin dosing, and artificial pancreas control algorithms. The aim of this paper is to propose an approach to describe CGM sensor error by exploiting n multiple simultaneous CGM recordings. The model of sensor error description includes a model of blood-to-interstitial glucose diffusion process, a linear time-varying model to account for calibration and sensor drift-in-time, and an autoregressive model to describe the additive measurement noise. Model orders and parameters are identified from the n simultaneous CGM sensor recordings and BG references. While the model is applicable to any CGM sensor, here, it is used on a database of 36 datasets of type 1 diabetic adults in which n = 4 Dexcom SEVEN Plus CGM time series and frequent BG references were available simultaneously. Results demonstrates that multiple simultaneous sensor data and proper modeling allow dissecting the sensor error into its different components, distinguishing those related to physiology from those related to technology. 

Farrell, A. S., Allen-Petersen, B., Daniel, C. J., Wang, X., Wang, Z., Rodriguez, S., et al. (2014). Targeting inhibitors of the tumor suppressor PP2A for the treatment of pancreatic cancer. *Molecular Cancer Research : MCR*,

Pancreatic cancer is a deadly disease that is usually diagnosed in the advanced stages when few effective therapies are available. Given the aggressive clinical course of this disease and lack of good treatment options, the development of new therapeutic agents for the treatment of pancreatic cancer is of the upmost importance. Several pathways shown to contribute to pancreatic cancer progression are negatively regulated by the tumor suppressor, protein phosphatase 2A (PP2A). Here, the endogenous inhibitors of PP2A, SET (also known as I2PP2A)

and Cancerous Inhibitor of PP2A (CIP2A), were shown to be overexpressed in human pancreatic cancer, contributing to decreased PP2A activity, and overexpression and stabilization of the oncoprotein c-Myc, a key PP2A target. Knockdown of SET or CIP2A increases PP2A activity, increases c-Myc degradation, and decreases the tumorigenic potential of pancreatic cancer cell lines both in vitro and in vivo. Moreover, treatment with a novel SET inhibitor, OP449, pharmacologically recapitulates the phenotypes and significantly reduces proliferation and tumorigenic potential of several pancreatic cancer cell lines, with an accompanying attenuation of cell growth and survival signaling. Furthermore, primary cells from pancreatic cancer patients were sensitive to OP449 treatment, indicating that PP2A regulated pathways are highly relevant to this deadly disease. Implications: The PP2A inhibitors SET and CIP2A are overexpressed in human pancreatic cancer and are important for pancreatic cancer cell growth and transformation; thus, antagonizing SET and/or CIP2A may be an innovative approach for the treatment of human pancreatic cancer.

Feuer, S. K., Liu, X., Donjacour, A., Lin, W., Simbulan, R. K., Giritharan, G., et al. (2014). Use of a mouse in vitro fertilization model to understand the developmental origins of health and disease hypothesis. *Endocrinology, 155*(5), 1956-1969.

The Developmental Origins of Health and Disease hypothesis holds that alterations to homeostasis during critical periods of development can predispose individuals to adult-onset chronic diseases such as diabetes and metabolic syndrome. It remains controversial whether preimplantation embryo manipulation, clinically used to treat patients with infertility, disturbs homeostasis and affects long-term growth and metabolism. To address this controversy, we have assessed the effects of in vitro fertilization (IVF) on postnatal physiology in mice. We demonstrate that IVF and embryo culture, even under conditions considered optimal for mouse embryo culture, alter postnatal growth trajectory, fat accumulation, and glucose metabolism in adult mice. Unbiased metabolic profiling in serum and microarray analysis of pancreatic islets and insulin sensitive tissues (liver, skeletal muscle, and adipose tissue) revealed broad changes in metabolic homeostasis, characterized by systemic oxidative stress and mitochondrial dysfunction. Adopting a candidate approach, we identify thioredoxin-interacting protein (TXNIP), a key molecule involved in integrating cellular nutritional and oxidative states with metabolic response,

as a marker for preimplantation stress and demonstrate tissue-specific epigenetic and transcriptional TXNIP misregulation in selected adult tissues. Importantly, dysregulation of TXNIP expression is associated with enrichment for H4 acetylation at the Txnip promoter that persists from the blastocyst stage through adulthood in adipose tissue. Our data support the vulnerability of preimplantation embryos to environmental disturbance and demonstrate that conception by IVF can reprogram metabolic homeostasis through metabolic, transcriptional, and epigenetic mechanisms with lasting effects for adult growth and fitness. This study has wide clinical relevance and underscores the importance of continued follow-up of IVF-conceived offspring.

Fleseriu, M. (2014). Recent advances in the medical treatment of cushing's disease. *F1000prime Reports*, *6*, 18.

Cushing's disease is a condition of hypercortisolism caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. While rare, it is associated with significant morbidity and mortality, which suggests that early and aggressive intervention is required. The primary, definitive therapy for patients with Cushing's disease in the majority of patients is pituitary surgery, generally performed via a transsphenoidal approach. However, many patients will not achieve remission or they will have recurrences. The consequences of persistent hypercortisolism are severe and, as such, early identification of those patients at risk of treatment failure is exigent. Medical management of Cushing's disease patients plays an important role in achieving long-term remission after failed transsphenoidal surgery, while awaiting effects of radiation or before surgery to decrease the hypercortisolemia and potentially reducing perioperative complications and improving outcome. Medical therapies include centrally acting agents, adrenal steroidogenesis inhibitors and glucocorticoid receptor blockers. Furthermore, several new agents are in clinical trials. To normalize the devastating disease effects of hypercortisolemia, it is paramount that successful patient disease management includes individualized, multidisciplinary care, with close collaboration between endocrinologists, neurosurgeons, radiation oncologists, and general surgeons. This commentary will focus on recent advances in the medical treatment of Cushing's, with a focus on newly approved ACTH modulators and glucocorticoid receptor blockers.

Freeman, B. E., Meyer, C., & Slifka, M. K. (2014). Anti-inflammatory cytokines directly inhibit innate but not adaptive CD8+ T cell functions. *Journal of Virology*,

Virus-specific CD8+ T cells provide classical adaptive immunity by responding to cognate peptide antigen, but they may also act in an "innate" capacity by responding directly to cytokine stimulation. Here, we examined regulation of these distinct T cell functions by anti-inflammatory cytokines (IL-4, IL-10, TGFbeta). Innate IFNgamma production by CD8+ T cells following exposure to IL-12+IL-18, IL-12+TNFalpha, or IL-12+IL-15 was inhibited by exposure to anti-inflammatory cytokines either before or shortly after stimulation. However, inhibition was not universal, as other activation parameters, including upregulation of CD25 and CD69, remained largely unaltered. In contrast, peptide-specific T cell responses were resistant to inhibition by anti-inflammatory cytokines. This was not due to down-regulation of cytokine receptor expression or an inability to signal through cytokine receptors since phosphorylation of STAT proteins remained intact. These results highlight key differences in cytokine-mediated regulation of innate and adaptive T cell functions, which may help balance effective antiviral immune responses while reducing T cell-mediated immunopathology. IMPORTANCE: This study demonstrates key differences between the regulation of "innate" and "adaptive" CD8+ T cell functions following activation by innate cytokines or viral peptide. Innate production of IFNgamma by CD8+ T cells following exposure to IL-12+IL-18, IL-12+TNFalpha, or IL-12+IL-15 was inhibited by exposure to anti-inflammatory cytokines (IL-4, IL-10, and TGFbeta). However, inhibition was not universal, as other activation parameters, including upregulation of CD25 and CD69, remained largely unaltered. In contrast, peptide-specific T cell responses were resistant to inhibition by anti-inflammatory cytokines. This distinct regulation of innate and adaptive T cell functions may serve to reduce T cell-mediated immunopathology while still allowing for effective antiviral responses at a site of infection.

Frias, A. E., Schabel, M. C., Roberts, V. H., Tudorica, A., Grigsby, P. L., Oh, K. Y., et al. (2014). Using dynamic contrast-enhanced MRI to quantitatively characterize maternal vascular organization in the primate placenta. *Magnetic Resonance in Medicine : Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*,

PURPOSE: The maternal microvasculature of the primate placenta is organized into 10-20

perfusion domains that are functionally optimized to facilitate nutrient exchange to support fetal growth. This study describes a dynamic contrast-enhanced magnetic resonance imaging method for identifying vascular domains and quantifying maternal blood flow in them. METHODS: A rhesus macaque on the 133rd day of pregnancy (G133, term = 165 days) underwent Doppler ultrasound procedures, dynamic contrast-enhanced magnetic resonance imaging and Cesarean-section delivery. Serial T1 -weighted images acquired throughout intravenous injection of a contrast reagent bolus were analyzed to obtain contrast reagent arrival time maps of the placenta. RESULTS: Watershed segmentation of the arrival time map identified 16 perfusion domains. The number and location of these domains corresponded to anatomical cotyledonary units observed following delivery. Analysis of the contrast reagent wave front through each perfusion domain enabled determination of volumetric flow, which ranged from 9.03 to 44.9 mL/s (25.2 +/- 10.3 mL/s). These estimates are supported by Doppler ultrasound results. CONCLUSIONS: The dynamic contrast-enhanced magnetic resonance imaging analysis described here provides quantitative estimates of the number of maternal perfusion domains in a primate placenta and estimates flow within each domain. Anticipated extensions of this technique are to the study placental function in non-human primate models of obstetric complications. Magn Reson Med, 2014. (c) 2014 Wiley Periodicals, Inc.

Gareau, D., Jacques, S., & Krueger, J. (2014). Monte Carlo modeling of pigmented lesions. *Photonic Therapeutics and Diagnostics X,* San Francisco, CA. , *8926.*

Colors observed in clinical dermoscopy are critical to diagnosis but the mechanisms that lead to the spectral components of diffuse reflectance are more than meets the eye: combinations of the absorption and scattering spectra of the biomolecules as well as the a structural effect of skin anatomy. We modeled diffuse remittance from skin based on histopathology. The optical properties of the tissue types were based on the relevant chromophores and scatterers. The resulting spectral images mimic the appearance of pigmented lesions quite well when the morphology is mathematically derived but limited when based on histopathology, raising interesting questions about the interaction between various wavelengths with various pathological anatomical features. © 2014 SPIE.

Genta, R. M., Hurrell, J. M., & Sonnenberg, A. (2014). Duodenal adenomas coincide with colorectal neoplasia. *Digestive Diseases and Sciences*,

Background and Aim Small case series have alluded to an association between sporadic duodenal adenomas and colorectal neoplasia. The strength of the association remains uncertain. This case-control study was designed to test this association in a large national pathology database. Methods This study, performed at Miraca Life Sciences, a specialized pathology laboratory that receives gastrointestinal biopsy specimens from outpatient centers throughout the US, included all subjects who underwent a bidirectional endoscopy with biopsy results from both procedures between January 2008 and December 2011. The association between duodenal and colonic neoplasms was investigated using odds ratios (OR) and their 95 % confidence intervals (CIs) derived from univariate and multivariate analyses. Results There were 203,277 patients who underwent bidirectional procedures within the study period (mean age 58 years, 58 % females). Duodenal adenomas were present in 537 patients (median age 65 years, 51 % females; OR for male sex 1.34, 95 % CI 1.13-1.59). Hyperplastic colon polyps were present in 30,205 and colon adenomas in 85,801 patients. Hyperplastic polyps were more common in patients with duodenal adenomas (1.45, 1.07-1.95). Patients with duodenal adenomas also had a significantly greater prevalence of all types of colonic adenomas (2.65, 2.16-3.25), particularly of advanced adenomas (4.30, 3.24-5.70) and colorectal cancer (3.13, 1.38-7.12). Duodenal adenomas were associated with an equally increased risk for left and right colon adenomas. Conclusions Patients with duodenal adenomas harbor an increased risk for any type of colonic neoplasm. This association may provide new insights into the general mechanisms underlying mucosal proliferation in the gastrointestinal tract. 

Gesuete, R., Kohama, S. G., & Stenzel-Poore, M. P. (2014). Toll-like receptors and ischemic brain injury. *Journal of Neuropathology and Experimental Neurology, 73*(5), 378-386.

Toll-like receptors (TLRs) are master regulators of innate immunity and play an integral role in the activation of inflammatory response during infections. In addition, TLRs influence the body's response to numerous forms of injury. Recent data have shown that TLRs play a modulating role in ischemic brain damage after stroke. Interestingly, their stimulation before ischemia induces a

tolerant state that is neuroprotective. This phenomenon, referred to as TLR preconditioning, is the result of the reprogramming of TLR response to ischemic injury. This review addresses the role of TLRs in brain ischemia and the activation of endogenous neuroprotective pathways in the setting of preconditioning. We highlight the protective role of interferon-related response and the potential site of action for TLR preconditioning involving the blood-brain barrier. Pharmacologic modulation of TLR activation to promote protection against stroke is a promising approach for the development of prophylactic and immediate therapies targeting ischemic brain injury.

Gil, Y., McWeeney, S., & Mason, C. E. (2013). Using semantic workflows to disseminate best practices and accelerate discoveries in multi-omic data analysis. *2013 AAAI Workshop*, Bellevue, WA. , *WS-13-09.* pp. 25-30.

The goal of our work is to enable omics analysis to be easily contextualized and interpreted for development of clinical decision aids and integration with Electronic Health Records (EHRs). We are developing a framework where common omics analysis methods are easy to reuse, analytic results are reproducible, and validation is enforced by the system based on characteristics of the data at hand. Our approach uses semantic workflows to capture multi-step omic analysis methods and annotate them with constraints that express appropriate use for algorithms and types of data. This paper describes our initial work to use semantic workflows to disseminate best practices, ensure valid use of analytic methods, and enable reproducibility of omics analyses. Key elements of this framework are that it is knowledge-rich with regard to parameters and constraints that impact the analyses, proactive in the use of this knowledge to guide users to validate and correct their analyses and dynamic/adaptive as data sets evolve and change, all features that are critical for successful integration of omics analyses in a clinical setting.



Giralt, S., Costa, L., Schriber, J., DiPersio, J., Maziarz, R., McCarty, J., et al. (2014). Optimizing autologous stem cell mobilization strategies to improve patient outcomes: Consensus guidelines and recommendations. *Biology of Blood and Marrow Transplantation*, *20*(3), 295-308.

Autologous hematopoietic stem cell transplantation (aHSCT) is a well-established treatment for malignancies such as multiple myeloma (MM) and lymphomas. Various changes in the field over

the past decade, including the frequent use of tandem aHSCT in MM, the advent of novel therapies for the treatment of MM and lymphoma, and the addition of new stem cell mobilization techniques, have led to the need to reassess current stem cell mobilization strategies. Mobilization failures with traditional strategies are common and result in delays in treatment and increased cost and resource utilization. Recently, plerixafor-containing strategies have been shown to significantly reduce mobilization failure rates, but the ideal method to maximize stem cell yields and minimize costs associated with collection has not yet been determined. A panel of experts convened to discuss the currently available data on autologous hematopoietic stem cell mobilization and transplantation and to devise guidelines to optimize mobilization strategies. Herein is a summary of their discussion and consensus. © 2014 American Society for Blood and Marrow Transplantation.

Gonçalves, F. T., Fridman, C., Pinto, E. M., Guevara-Aguirre, J., Shevah, O., Rosembloom, A. L., et al. (2014). The E180splice mutation in the GHR gene causing laron syndrome: Witness of a sephardic jewish exodus from the iberian peninsula to the new world? *American Journal of Medical Genetics, Part A, 164*(5), 1204-1208.

Laron syndrome (LS) is a genetic disorder caused by mutations in the growth hormone receptor (GHR) gene. The most frequent GHR mutation is E180splice (rs121909360), which was initially found in an inbred population of Spanish descent in Ecuador and subsequently in Israel, Brazil, Chile, and the United States. The aim of the present study is to determine if the E180splice mutation arose from a common origin. We studied 22 patients with LS from Ecuador, Israel (of Moroccan origin), Brazil, Chile, and the United States (of Mexican origin) who were homozygous for the E180splice mutation and compared them to control individuals for markers surrounding the GHR, intragenic polymorphisms, and Y-chromosome STR. An identical haplotype was found in all but one of the subjects carrying the E180splice mutation: D5S665: 150/150; D5S2082: 192/192; D5S2087: 246/246; rs6179 G/G; and rs6180 C/C. One patient differed from the others only at D5S2082 (168/192). This haplotype is rare (~1%) in control individuals and confirmed that the E180splice-associated haplotype was not derived from independent origins but represented recombination from a common ancestor. The analysis of paternal lineage markers showed that 50% belong to haplogroup R1b (found in Portugal and Spain) and 40% to

haplogroups J and E (typical in the Middle East and in Eastern European Jews). The germline E180Splice mutation appears to have originated from a single common ancestor. The presence of Y-chromosome markers associated with Sephardic populations in persons harboring the E180splice mutation provides genetic evidence in support of the historical tracking of the exodus of this specific population. © 2014 Wiley Periodicals, Inc.

Grados Luyando, M. D. C., Bar, A., Snavely, N., Jacques, S., & Gareau, D. S. (2014). Multimodal confocal mosaics enable high sensitivity and specificity in screening of in situ squamous cell carcinoma. *Multimodal Biomedical Imaging IX*, San Francisco, CA. , *8937.*

Screening cancer in excision margins with confocal microscopy may potentially save time and cost over the gold standard histopathology (H and E). However, diagnostic accuracy requires sufficient contrast and resolution to reveal pathological traits in a growing set of tumor types. Reflectance mode images structural details due to microscopic refractive index variation. Nuclear contrast with acridine orange fluorescence provides enhanced diagnostic value, but fails for in situ squamous cell carcinoma (SCC), where the cytoplasm is important to visualize. Combination of three modes [eosin (Eo) fluorescence, reflectance (R) and acridine orange (AO) fluorescence] enable imaging of cytoplasm, collagen and nuclei respectively. Toward rapid intra-operative pathological margin assessment to guide staged cancer excisions, multimodal confocal mosaics can image wide surgical margins (~1cm) with sub-cellular resolution and mimic the appearance of conventional H and E. Absorption contrast is achieved by alternating the excitation wavelength: 488nm (AO fluorescence) and 532nm (Eo fluorescence). Superposition and false-coloring of these modes mimics H and E, enabling detection of the carcinoma in situ in the epidermal layer The sum mosaic Eo+R is false-colored pink to mimic eosins' appearance in H and E, while the AO mosaic is false-colored purple to mimic hematoxylins' appearance in H and E. In this study, mosaics of 10 Mohs surgical excisions containing SCC in situ and 5 containing only normal tissue were subdivided for digital presentation equivalent to 4X histology. Of the total 16 SCC in situ multimodal mosaics and 16 normal cases presented, two reviewers made 1 and 2 (respectively) type-2 errors (false positives) but otherwise scored perfectly when using the confocal images to screen for the presence of SCC in situ as compared to the gold standard histopathology. Limitations to precisely mimic H and E included occasional elastin staining by AO.

These results suggest that confocal mosaics may effectively guide staged SCC excisions in skin and other tissues. © 2014 Copyright SPIE.

Grant, M. J., Didier, R. A., Stevens, J. S., Beyder, D. D., Hunter, J. G., Thomas, C. R., et al. (2014). Radiation-induced liver disease as a mimic of liver metastases at serial PET/CT during neoadjuvant chemoradiation of distal esophageal cancer. *Abdominal Imaging*,

PURPOSE: To determine the frequency and appearance of radiation-induced liver disease on PET/CT in patients undergoing serial imaging during neoadjuvant chemoradiation of distal esophageal cancer. MATERIALS AND METHODS: In this IRB-approved, HIPAA-compliant retrospective analysis, we identified 112 patients with distal esophageal cancer treated by neoadjuvant chemoradiation who had serial PET/CT imaging available for review. Two readers reviewed all studies in consensus and recorded those cases where new foci of visually detectable increased FDG avidity appeared in the liver during therapy. The etiology of such foci was determined from corresponding findings at CT or MRI, by hepatic biopsy during surgery, by characteristic evolution on post-operative imaging, or by a combination of these methods. RESULTS: New foci of FDG avidity developed in the liver during neoadjuvant therapy in 10 of 112 (9%) patients, of whom nine (8%) were determined to have radiation-induced liver disease based on further imaging and/or biopsy and one of whom had developed interval metastatic disease based on biopsy. In the cases of radiation-induced liver disease, the abnormal foci were found only in the caudate and left hepatic lobes, near the primary tumor, while the patient who developed interval metastatic disease had involvement of the inferior right hepatic lobe, remote from the radiation therapy field. CONCLUSION: New foci of increased FDG avidity are commonly seen in the caudate and left hepatic lobes of the liver during neoadjuvant chemoradiation of distal esophageal cancer, and these findings generally reflect radiation-induced liver disease rather than metastatic disease.

Grobman, W. A., Bailit, J. L., Rice, M. M., Wapner, R. J., Reddy, U. M., Varner, M. W., et al. (2014). Frequency of and factors associated with severe maternal morbidity. *Obstetrics and Gynecology*, *123*(4), 804-810.

OBJECTIVE: To estimate the frequency of severe maternal morbidity, assess its underlying

etiologies, and develop a scoring system to predict its occurrence. METHODS: This was a secondary analysis of a Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network cohort of 115,502 women and their neonates born in 25 hospitals across the United States over a 3-year period. Women were classified as having severe maternal morbidity according to a scoring system that takes into account the occurrence of red blood cell transfusion (more than three units), intubation, unanticipated surgical intervention, organ failure, and intensive care unit admission. The frequency of severe maternal morbidity was calculated and the underlying etiologies determined. Multivariable analysis identified patient factors present on admission that were independently associated with severe maternal morbidity; these were used to develop a prediction model for severe maternal morbidity. RESULTS: Among 115,502 women who delivered during the study period, 332 (2.9/1,000 births, 95% confidence interval 2.6-3.2) experienced severe maternal morbidity. Postpartum hemorrhage was responsible for approximately half of severe maternal morbidity. Multiple patient factors were found to be independently associated with severe maternal morbidity and were used to develop a predictive model with an area under the receiver operating characteristic curve of 0.80. CONCLUSION: Severe maternal morbidity occurs in approximately 2.9 per 1,000 births, is most commonly the result of postpartum hemorrhage, and occurs more commonly in association with several identifiable patient characteristics. 

Gross, N. D., Bauman, J. E., Gooding, W. E., Denq, W. H., Thomas, S. M., Wang, L., et al. (2014). Erlotinib, erlotinib-sulindac vs. placebo: A randomized, double-blind, placebo-controlled window trial in operable head and neck cancer. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,

PURPOSE: The epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2) pathways are upregulated in head and neck squamous cell carcinoma (HNSCC). Preclinical models indicate synergistic anti-tumor activity from dual blockade. We conducted a randomized, double-blind, placebo-controlled window trial of erlotinib, an EGFR inhibitor; erlotinib plus sulindac, a non-selective COX inhibitor, vs. placebo. EXPERIMENTAL DESIGN: Patients with untreated, operable Stage II-IVb HNSCC were randomized 5:5:3 to erlotinib, erlotinib-sulindac, or placebo. Tumor

specimens were collected before and after 7-14 days of treatment. The primary endpoint was change in Ki-67 proliferation index. We hypothesized an ordering effect in Ki-67 reduction: erlotinib-sulindac > erlotinib > placebo. We evaluated tissue microarrays by immunohistochemistry for pharmacodynamic modulation of EGFR and COX-2 signaling intermediates. RESULTS: From 2005-2009, 47 patients were randomized for the target 39 evaluable patients. Thirty-four tumor pairs were of sufficient quality to assess biomarker modulation. Ki-67 was significantly decreased by erlotinib or erlotinib-sulindac (omnibus comparison, two-sided Kruskal-Wallis, p=0.04). Wilcoxon pairwise contrasts confirmed greater Ki-67 effect in both erlotinib groups (erlotinib-sulindac vs. placebo p=0.043; erlobinib vs. placebo, p=0.027). There was a significant trend in ordering of Ki-67 reduction: erlotinib-sulindac > erlotinib > placebo (two-sided exact Jonckheere-Terpstra, p =0.0185). Low baseline pSrc correlated with greater Ki-67 reduction (R2 = .312, p = 0.024). CONCLUSIONS: Brief treatment with erlotinib significantly decreased proliferation in HNSCC, with additive effect from sulindac. Efficacy studies of dual EGFR-COX inhibition are justified. pSrc is a potential resistance biomarker for anti-EGFR therapy, and warrants investigation as a molecular target.

Gross, N. D., & Holsinger, C. (2014). Robotic surgery of the head and neck. *Otolaryngologic Clinics of North America*,

Gruber, A. (2014). The role of the contact pathway in thrombus propagation. *Thrombosis Research, 133 Suppl 1*, S45-7.

The continued search for the ideal antithrombotic agent that would prevent or reduce thrombus growth inside blood vessels without an effect on the essential hemostatic functions of blood, including extraluminal thrombin generation and platelet activation, has been going in new directions in the past decade. These directions include studies suggesting that activation of the intrinsic coagulation cascade through contact activation of factor XII, and the resultant thrombin generation is a pathologic event that leads to undesirable consequences. Recent animal studies of contact pathway inhibitors in experimental thrombogenesis suggest that the contact activation pathway of blood coagulation may play a pathogenic role in thrombosis, and pharmacologic inhibition of contact activation may have antithrombotic effects. Development of reasonably

potent selective inhibitors of contact activation pathway components or activities now allow for the conduct of studies in various animal species, including primates. These studies have generated interesting data that now support the hypothesis that thrombogenesis in humans may also involve the pathological activation of the intrinsic coagulation cascade. Moreover, baboons, mice, and rabbits, pretreated with antibodies that selectively inhibit factor XII activation, procoagulant factor XIIa activity, or all enzymatic activities of factor XIIa show significantly reduced propensity for occlusive thrombus propagation in various models of acute thrombogenesis on vascular grafts, membrane oxygenators, and even on injured arteries. Since contact activation of blood does not play a demonstrable role in normal hemostasis, and there has been no evidence generated to date suggesting that activation of factor XII has a physiologic function, current research now supports the original concept, developed over 2 decades ago, that temporal pharmacologic inhibition of thrombin generation through the contact pathway may have therapeutic potential and could produce beneficial antithrombotic activities without hemostasis impairment.

Grygoryev, D., Dan, C., Gauny, S., Eckelmann, B., Ohlrich, A. P., Connolly, M., et al. (2014). Autosomal mutants of proton-exposed kidney cells display frequent loss of heterozygosity on nonselected chromosomes. *Radiation Research*,

High-energy protons found in the space environment can induce mutations and cancer, which are inextricably linked. We hypothesized that some mutants isolated from proton-exposed kidneys arose through a genome-wide incident that causes loss of heterozygosity (LOH)-generating mutations on multiple chromosomes (termed here genomic LOH). To test this hypothesis, we examined 11 pairs of nonselected chromosomes for LOH events in mutant cells isolated from the kidneys of mice exposed to 4 or 5 Gy of 1 GeV protons. The mutant kidney cells were selected for loss of expression of the chromosome 8-encoded Aprt gene. Genomic LOH events were also assessed in Aprt mutants isolated from isogenic cultured kidney epithelial cells exposed to 5 Gy of protons in vitro. Control groups were spontaneous Aprt mutants and clones isolated without selection from the proton-exposed kidneys or cultures. The in vivo results showed significant increases in genomic LOH events in the Aprt mutants from proton-exposed kidneys when compared with spontaneous Aprt mutants and when compared with nonmutant (i.e.,

nonselected) clones from the proton-exposed kidneys. A bias for LOH events affecting chromosome 14 was observed in the proton-induced Aprt mutants, though LOH for this chromosome did not confer increased radiation resistance. Genomic LOH events were observed in Aprt mutants isolated from proton-exposed cultured kidney cells; however the incidence was fivefold lower than in Aprt mutants isolated from exposed intact kidneys, suggesting a more permissive environment in the intact organ and/or the evolution of kidney clones prior to their isolation from the tissue. We conclude that proton exposure creates a subset of viable cells with LOH events on multiple chromosomes, that these cells form and persist in vivo, and that they can be isolated from an intact tissue by selection for a mutation on a single chromosome.

Guo, C., Sinnott, B., Niu, B., Lowry, M. B., Fantacone, M. L., & Gombart, A. F. (2014). Synergistic induction of human cathelicidin antimicrobial peptide gene expression by vitamin D and stilbenoids. *Molecular Nutrition and Food Research, 58*(3), 528-536.

Scope: The cathelicidin antimicrobial peptide (CAMP) gene is induced by 1α,25-dihydroxyvitamin D3 (1α,25(OH)2D3), lithocholic acid, curcumin, nicotinamide, and butyrate. Discovering additional small molecules that regulate its expression will identify new molecular mechanisms involved in CAMP regulation and increase understanding of how diet and nutrition can improve immune function. Methods and results: We discovered that two stilbenoids, resveratrol and pterostilbene, induced CAMP promoter-luciferase expression. Synergistic activation was observed when either stilbenoid was combined with 1α,25(OH)2D3. Both stilbenoids increased CAMP mRNA and protein levels in the monocyte cell line U937 and synergy was observed in both U937 and the keratinocyte cell line, HaCaT. Inhibition of resveratrol targets sirtuin-1, cyclic AMP production and the c-Jun N-terminal, phosphoinositide 3 and AMP-activated kinases did not block induction of CAMP by resveratrol or synergy with 1α,25(OH)2D3. Nevertheless, inhibition of the extracellular signal regulated 1/2 and p38 mitogen-activated protein kinases, increased CAMP gene expression in combination with 1α,25(OH)2D3 suggesting that inhibition of these kinases by resveratrol may explain, in part, its synergy with vitamin D. Conclusion: Our findings demonstrate for the first time that stilbenoid compounds may have the potential to boost the innate immune response by increasing CAMP gene expression, particularly in combination with 1α,25(OH)2D3. 

Haghighi, M., Akcakaya, M., Orhan, U., Erdogmus, D., Okeny, B., & Fried-Okeny, M. (2013). Initial assessment of artifact filtering for rsvp keyboard™. *2013 IEEE Signal Processing in Medicine and Biology Symposium, SPMB 2013,* Brooklyn, NY.

RSVP KeyboardTM is an electroencephalography (EEG)-based spelling interface that uses evoked response potential classification with the help of language models. As in any brain computer interface, severe physiological and environmental signal artifacts that affect signal quality in EEG are a detriment to performance. To alleviate the negative effects of such artifacts on RSVP KeyboardTM, we implemented a filter that is based on an existing methodology from the literature. Using statistical modeling of pre-recorded EEG that includes three types of artifacts intentionally generated by operators, we perform Monte Carlo simulations of copy-phrase tasks and analyze the effect of artifact filtering on estimated typing performance. The presented results demonstrate an evidence against the usability of the tested method for online artifact reduction applications.

Hartung, D. M., Zarin, D. A., Guise, J. -., McDonagh, M., Paynter, R., & Helfand, M. (2014). Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Annals of Internal Medicine, 160*(7), 477-483.

Background: ClinicalTrials.gov requires reporting of result summaries for many drug and device trials. Purpose: To evaluate the consistency of reporting of trials that are registered in the ClinicalTrials.gov results database and published in the literature. Data Sources: ClinicalTrials.gov results database and matched publications identified through ClinicalTrials.gov and a manual search of 2 electronic databases. Study Selection: 10% random sample of phase 3 or 4 trials with results in the ClinicalTrials.gov results database, completed before 1 January 2009, with 2 or more groups. Data Extraction: One reviewer extracted data about trial design and results from the results database and matching publications. A subsample was independently verified. Data Synthesis: Of 110 trials with results, most were industrysponsored, parallel-design drug studies. The most common inconsistency was the number of secondary outcome measures reported (80%). Sixteen trials (15%) reported the primary outcome description inconsistently, and 22 (20%) reported the primary outcome value inconsistently. Thirty-eight trials inconsistently reported the number of individuals with a serious adverse event (SAE); of these, 33 (87%)

reported more SAEs in ClinicalTrials.gov. Among the 84 trials that reported SAEs in ClinicalTrials.gov, 11 publications did not mention SAEs, 5 reported them as zero or not occurring, and 21 reported a different number of SAEs. Among 29 trials that reported deaths in ClinicalTrials.gov, 28% differed from the matched publication. Limitation: Small sample that included earliest results posted to the database. Conclusion: Reporting discrepancies between the ClinicalTrials.gov results database and matching publications are common. Which source contains the more accurate account of results is unclear, although ClinicalTrials.gov may provide a more comprehensive description of adverse events than the publication. © 2014 American College of Physicians.

Hatch, B. A., DeVoe, J. E., Lapidus, J. A., Carlson, M. J., & Wright, B. J. (2014). Citizenship documentation requirement for medicaid eligibility: Effects on oregon children. *Family Medicine*, *46*(4), 267-275.

BACKGROUND AND OBJECTIVES: The Deficit Reduction Act (DRA) of 2005 mandated Medicaid beneficiaries to document citizenship. Using a prospective cohort (n=104,375), we aimed to (1) determine characteristics of affected children, (2) describe effects on health insurance coverage and access to needed health care, and (3) model the causal relationship between this new policy, known determinants of health care access, and receipt of needed health care. METHODS: We identified a stratified random sample of children shortly after the DRA was implemented and used state records and surveys to compare three groups: children denied Medicaid for inability to document citizenship, children denied for other reasons, and children accepted for coverage. To combat survey nonresponse, we used Medicaid records to identify differences between responders and nonrespondents and created survey weights to account for these differences. Weighted simple and multivariable logistic regression described the complete, originally identified population. RESULTS: Children denied Medicaid for inability to document citizenship were likely to be US citizens, were medically and socially more vulnerable than their peers, and went on to have gaps in health insurance coverage and unmet health care needs. The DRA led to persistent loss of insurance coverage, which decreased access to needed health care. Having a usual source of care was an effect modifier in this relationship. CONCLUSIONS: Our findings demonstrate the

negative consequences of the DRA and support the use of automated methods of citizenship verification allowed under the Patient Protection and Affordable Care Act.

Heckler, A. M., Sung, J., Watters, S., Martinez Acevedo, A., Conlin, M., & Skoog, S. (2014). The long-term incidence of urinary tract infection after endoscopic management of vesicoureteral reflux. *Urology*,

OBJECTIVE: To evaluate the long-term urinary tract infection (UTI) rates after endoscopic correction of vesicoureteral reflux and the possible risk factors for urinary infection. MATERIALS AND METHODS: A retrospective study of patients who underwent endoscopic management of vesicoureteral reflux at a single institution from 2001 to 2011 was performed. Patients were followed up for a minimum of 1 year. Voiding cystourethrograms were completed 3 months postoperatively. UTI questionnaire pertaining to the patient's UTI history before and after the surgery was mailed to each patient. Data were first evaluated looking only at culture-confirmed UTIs, and a second analysis included all patient-reported and culture-confirmed urinary infections. Factors considered in the analysis included sex, age, preoperative dimercaptosuccinic acid (DMSA) scan, reflux on postoperative voiding cystourethrogram, voiding dysfunction, and preoperative reflux grade. RESULTS: Data on 175 patients for a minimum of 1 year were collected. There were 34 of 175 confirmed UTIs after endoscopic management, and 11 confirmed febrile UTIs. There were no significant predictors of febrile or afebrile UTIs in this group. Fifty-three of 175 patients (30%) experienced any UTI, 19 of which were febrile (10%). In this group, recurrent reflux was the only significant predictor of UTI (P = .03) and febrile UTIs (P = .04). Patients with more UTIs preoperatively were more likely to have a postoperative febrile UTI. CONCLUSION: Rates of UTI and febrile UTI in endoscopic management are similar and no better than those for open ureteral reimplantation. Longer follow-up suggests an association of recurrent reflux and preoperative UTI rates as predictors of postoperative febrile UTIs. These patients benefit from closer postoperative observation.

Heppner, K. M., & Tong, J. (2014). Regulation of glucose metabolism by the ghrelin system: Multiple players and multiple actions. *European Journal of Endocrinology / European Federation of Endocrine Societies*,

Ghrelin is a 28-amino acid peptide secreted mainly from the X/A-like cells of the stomach. Ghrelin is found in circulation in both a des-acyl (dAG) and acyl form (AG). Acylation is catalyzed by the enzyme ghrelin O-acyltransferase (GOAT). AG acts on the growth hormone secretagogue receptor (GHSR) in the central nervous system (CNS) to promote feeding and adiposity, and also acts on GHSR in the pancreas to inhibit glucose-stimulated insulin secretion. These well-described actions of AG have made it a popular target for obesity and type 2 diabetes (T2DM) pharmacotherapies. However, despite the lack of a cognate receptor, dAG appears to have gluco-regulatory action, which adds an additional layer of complexity to ghrelin's regulation of glucose metabolism. This review discusses the current literature on the gluco-regulatory action of the ghrelin system (dAG, AG, GHSR and GOAT) with specific emphasis aimed towards distinguishing AG versus dAG action.

Hersh, S., Megregian, M., & Emeis, C. (2014). Intermittent auscultation of the fetal heart rate during labor: An opportunity for shared decision making. *Journal of Midwifery and Women's Health*, Electronic fetal heart rate monitoring is the most common form of intrapartal fetal assessment in the United States. Intermittent auscultation of the fetal heart rate is an acceptable option for low-risk laboring women, yet it is underutilized in the hospital setting. Several expert organizations have proposed the use of intermittent auscultation as a means of promoting physiologic childbirth. Within a shared decision-making model, the low-risk pregnant woman should be presented with current evidence about options for fetal heart rate assessment during labor. © 2014 by the American College of Nurse-Midwives.

Hetts, S. W., Turk, A., English, J. D., Dowd, C. F., Mocco, J., Prestigiacomo, C., et al. (2014). Stent-assisted coiling versus coiling alone in unruptured intracranial aneurysms in the matrix and platinum science trial: Safety, efficacy, and mid-term outcomes. *American Journal of Neuroradiology*, *35*(4), 698-705.

BACKGROUND AND PURPOSE: Stent-assisted coiling may result in less aneurysm recanalization but more complications than coiling alone. We evaluated outcomes of coiling with and without stents in the multicenter Matrix and Platinum Science Trial. MATERIALS AND METHODS: All patients in the Matrix and Platinum Science Trial with unruptured intracranial aneurysms treated

per protocol were included. Baseline patient and aneurysm characteristics, procedural details, neurologic outcomes, angiographic outcomes, and safety data were analyzed. RESULTS: Overall, 137 of 361 (38%) patients were treated with a stent. Stent-coiled aneurysms had wider necks (≥4mmin 62% with stents versus 33% without, P < .0001) and lower dome-to-neck ratios (1.3 versus 1.8, P < .0001). Periprocedural serious adverse events occurred infrequently in those treated with and without stents (6.6% versus 4.5%, P = .39). At 1 year, total significant adverse events, mortality, and worsening of mRS were similar in treatment groups, but ischemic strokes were more common in stent-coiled patients than in coiled patients (8.8% versus 2.2%, P = .005). However, multivariate analysis confirmed that at 2 years after treatment, prior cerebrovascular accident (OR, 4.7; P = .0089) and aneurysm neck width ≥4mm(OR, 4.5; P = .02) were the only independent predictors of ischemic stroke. Stent use was not an independent predictor of ischemic stroke at 2 years (OR, 1.1; P = .94). Stent use did not predict target aneurysm recurrence at 2 years, but aneurysm dome size ≥10 mm (OR, 9.94; P < .0001) did predict target aneurysm recurrence. CONCLUSIONS: Stent-coiling had similar outcomes as coiling despite stented aneurysms having more difficult morphology than coiled aneurysms. Increased ischemic events in stent-coiled aneurysms were attributable to baseline risk factors and aneurysm morphology.

Hills, W. L., Nassef, A. H., Grafe, M. R., Weissman, J. L., Moster, S. J., Falardeau, J., et al. (2014). Homonymous hemianopia due to erdheim-chester disease. *Journal of Neuro-Ophthalmology : The Official Journal of the North American Neuro-Ophthalmology Society*,
: Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis typically affecting multiple organ systems. We report 2 patients who presented with homonymous hemianopia and were ultimately diagnosed with biopsy-confirmed ECD. We review the spectrum of ECD and its treatment as well as histopathological and immunohistochemical differentiation from other histiocytic disorders.

Högler, W., Martin, D. D., Crabtree, N., Nightingale, P., Tomlinson, J., Metherell, L., et al. (2014). IGFALS gene dosage effects on serum IGF-I and glucose metabolism, body composition, bone growth in length and width, and the pharmacokinetics of recombinant human IGF-I

administration. *Journal of Clinical Endocrinology and Metabolism*, *99*(4), E703-E712.

Context: Acid labile subunit (ALS) deficiency, caused by IGFALS mutations, is a subtype of primary IGF-I deficiency (PIGFD) and has been associated with insulin resistance (IR) and osteopenia. Whether patients respond to recombinant human IGF-I (rhIGF-I) is unknown. Objective and Design: This study determined the 14-hour pharmacokinetic response of free and total IGF-I and IGF binding protein 3 (IGFBP-3) to a single sc dose of rhIGF-I (120-g/kg) in four ALS-deficient patients, compared with severe PIGFD, moderate PIGFD, and controls. Intravenous glucose tolerance tests, fasting bloodlevels,dual-energyX-rayabsorptiometry,peripheralquantitativecomputedtomography,andmetacarpal radiogrammetry were performed in the four patients and 12 heterozygous family members. Results: IGF-I and IGFBP-3 increased above baseline ($P < .05$) for 2.5 hours, returning to baseline 7 hours after rhIGF-I injection. Mean (SD) IGF-I Z-score increased by 2.49 (0.90), whereas IGFBP-3 Z-score increased by 0.57 (0.10) only. IGF-I elimination rates in ALS deficiency were similar, but the IGF-I increment was lower than those for severe PIGFD. Significant gene dosage effects were found for all IGF-I peptides, height, forearm muscle size,andmetacarpal width.Boneanalysisshowedthat ALS deficiency creates a phenotype of slender bones with normal size-corrected density. Abnormal glucose handling and IR was found in three of four patients and 6 of 12 carriers. Conclusions: These gene dosage effects demonstrate that one functional IGFALS allele is insufficient to maintain normal ALS levels, endocrine IGF-I action, full growth potential, muscle size, and periosteal expansion. Similar gene dosage effects may exist for parameters of IR. Despite similar IGF-I elimination comparedwith severe PIGFD, ALS-deficient patients cannotmountasimilar response. Alternativeways of rhIGF-I administration should be sought. Copyright © 2014 by the Endocrine Society.

Holliday, E. B., Jagsi, R., Wilson, L. D., Choi, M., Thomas, C. R.,Jr, & Fuller, C. D. (2014). Gender differences in publication productivity, academic position, career duration, and funding among u.s. academic radiation oncology faculty. *Academic Medicine : Journal of the Association of American Medical Colleges*, *89*(5), 767-773.

PURPOSE: This study aimed to analyze gender differences in rank, career duration, publication productivity, and research funding among radiation oncologists at U.S. academic institutions.

METHOD: For 82 domestic academic radiation oncology departments, the authors identified current faculty and recorded their academic rank, degree, and gender. The authors recorded bibliographic metrics for physician faculty from a commercially available database (Scopus, Elsevier BV), including numbers of publications from 1996 to 2012 and h-indices. The authors then concatenated these data with National Institutes of Health (NIH) funding per Research Portfolio Online Reporting Tools. The authors performed descriptive and correlative analyses, stratifying by gender and rank. RESULTS: Of 1,031 faculty, 293 (28%) women and 738 (72%) men, men had a higher median m-index, 0.58 (range 0-3.23) versus 0.47 (0-2.5) ($P < .05$); h-index, 8 (0-59) versus 5 (0-39) ($P < .05$); and publication number, 26 (0-591) versus 13 (0-306) ($P < .05$). Men were more likely to be senior faculty and receive NIH funding. After stratifying for rank, these differences were largely nonsignificant. On multivariate analysis, there were correlations between gender, career duration and academic position, and h-index ($P < .01$). CONCLUSIONS: Determinants of a successful career in academic medicine are multifactorial. Data from radiation oncologists show a systematic gender association, with fewer women achieving senior faculty rank. However, women achieving seniority have productivity metrics comparable to those of male counterparts. This suggests that early career development and mentorship of female faculty may narrow productivity disparities.

Huckans, M., Fuller, B. E., Olavarria, H., Sasaki, A. W., Chang, M., Flora, K. D., et al. (2014). Multi-analyte profile analysis of plasma immune proteins: Altered expression of peripheral immune factors is associated with neuropsychiatric symptom severity in adults with and without chronic hepatitis C virus infection. *Brain and Behavior, 4*(2), 123-142.

BackgroundThe purpose of this study was to characterize hepatitis C virus (HCV)-associated differences in the expression of 47 inflammatory factors and to evaluate the potential role of peripheral immune activation in HCV-associated neuropsychiatric symptoms-depression, anxiety, fatigue, and pain. An additional objective was to evaluate the role of immune factor dysregulation in the expression of specific neuropsychiatric symptoms to identify biomarkers that may be relevant to the treatment of these neuropsychiatric symptoms in adults with or without HCV. MethodsBlood samples and neuropsychiatric symptom severity scales were collected from HCV-infected adults (HCV+, n = 39) and demographically similar noninfected controls (HCV-, n = 40).

Multi-analyte profile analysis was used to evaluate plasma biomarkers. ResultsCompared with HCV- controls, HCV+ adults reported significantly (P the LDC) significantly correlated with depression, anxiety, and pain. Within the total sample, neuropsychiatric symptom severity was significantly predicted by protein signatures consisting of 4-10 plasma immune factors; protein signatures significantly accounted for 19-40% of the variance in depression, anxiety, fatigue, and pain. ConclusionsOverall, the results demonstrate that altered expression of a network of plasma immune factors contributes to neuropsychiatric symptom severity. These findings offer new biomarkers to potentially facilitate pharmacotherapeutic development and to increase our understanding of the molecular pathways associated with neuropsychiatric symptoms in adults with or without HCV.

Hunsberger, M., McGinnis, P., Smith, J., Beamer, B. A., & O'Malley, J. (2014). Elementary school children's recess schedule and dietary intake at lunch: A community-based participatory research partnership pilot study. *BMC Public Health*, *14*(1)

Background: School recess before lunch (e.g., reverse recess) has been suggested as a means to improve dietary intake and classroom behavior but limited research explores this school-based policy. This pilot study tests the impact of recess scheduling on dietary intake at school lunch. Methods. A mixed methods approach included assessment of dietary intake assessed by measured plate waste on five non-consecutive days at Madras Elementary School, Madras, Oregon, United States (n = 104 intervention; 157 controls). Subjects included primary school children in grades kindergarten, first and second. Logistic regression was used to test associations between recess timing and dietary intake. Four focus groups involving teachers and staff explored reactions to the intervention. Qualitative data was transcribed verbatim and assessed for key themes. Results: Milk consumption was 1.3 oz greater in the intervention group (5.7 oz vs. 4.4 oz); and 20% more of the intervention participants drank the entire carton of milk (42% vs. 25%, $p < 0.0001$). Intervention participants were 1.5 times more likely to meet the nutritional guidelines for calcium (≥267 mg, $p = 0.01$) and fat (≤30% of total energy, $p = 0.02$). Consumption of entrees, vegetables, and fruits did not differ between groups. Teachers perceived recess before lunch beneficial to classroom behavior and readiness to concentrate following lunch. Conclusions: The recess before lunch intervention yielded increased milk consumption; the

nutritional and social benefits observed warrant policy change consideration. Future research should assess the impact of recess before lunch in larger districts. © 2014 Hunsberger et al.; licensee BioMed Central Ltd.

Hunter, J. (2014). The world journal of surgery welcomes new associate editors. *World Journal of Surgery*,

Ishii, T., McElhinney, D. B., Harrild, D. M., Marcus, E. N., Sahn, D. J., Truong, U., et al. (2014). Ventricular strain in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome before and after prenatal aortic valvuloplasty. *Fetal Diagnosis and Therapy*, *35*(1), 18-26. Objective: The impact of prenatal intervention on fetal cardiac function has not been well defined. We assessed standard ventricular function parameters and strain in fetuses with evolving hypoplastic left heart syndrome (HLHS) treated with fetal aortic valvuloplasty (fAVP). Methods: Fetuses with valvar aortic stenosis that underwent fAVP were studied. Echocardiographic images prior to intervention (Pre), within 1 week after fAVP (Post), and at the last prenatal follow-up examination (FU) were analyzed. Left ventricular (LV) circumferential (LVCS) and longitudinal strain (LVLS), right ventricular (RV) longitudinal strain (RVLS), and LV end-diastolic dimension Z-scores (LVIDD-Z) were documented and compared according to postnatal outcome. Results: Among 57 fetuses studied, the postnatal outcome was biventricular in 23 and univentricular in 34. Prior to fAVP, strain was <4 in most cases, regardless of outcome. Biventricular fetuses had higher LVCS and LVLS segmental strain than univentricular fetuses. Among fetuses with a biventricular outcome, LVCS and LVLS increased as LVIDD-Z decreased in late gestation, whereas LVCS and LVLS remained <4 in univentricular fetuses, although the LVIDD-Z decreased to <0 in all cases. Septal RVLS increased after fAVP in the biventricular but not the univentricular outcome group. Conclusion: In utero aortic valve dilation appears to have a beneficial effect on both LV and RV function in some fetuses with evolving HLHS. © 2013 S. Karger AG, Basel.

Jacobs, J. V., Nutt, J. G., Carlson-Kuhta, P., Allen, R., & Horak, F. B. (2014). Dual tasking during postural stepping responses increases falls but not freezing in people with parkinson's disease. *Parkinsonism and Related Disorders*,

Purpose: Although falls in people with Parkinson's disease (PD) associate with dual tasking and

freezing of gait (FoG), it is not known whether falls during dual tasking are due to FoG. This study investigated the effects of a cognitive task on the occurrence of falls and FoG when subjects with PD step in response to a postural perturbation. Methods: Ten subjects with PD and a history of FoG as well as 10 age-matched subjects without PD stepped in response to large, backward displacements of the support surface, with and without performing a fluency task of listing items in a category. Subjects with PD performed the task in the "off" and "on" dopaminergic medication states. We recorded the percentage of trials with FoG (a lack of step in response to the perturbation), foot-lift latencies, and trials with falls into a safety harness. Results: Dual tasking significantly increased the incidence of falls in people with PD, but subjects without PD did not fall in any condition. Dual tasking did not significantly increase trials without steps or foot-lift latencies. Falls were often coincident with a lack of step (FoG) in the single-task condition, but the increased falls with dual tasking occurred on trials with steps. Levodopa tended to decrease FoG and falls with or without dual tasking. However, medication did not significantly alter the effects of dual tasking on FoG or falls. Conclusions: For people with PD and FoG, forward falls may not always be caused by FoG, particularly under attention-distracting conditions. 

Jia, Y., Bailey, S. T., Wilson, D. J., Tan, O., Klein, M. L., Flaxel, C. J., et al. (2014). Quantitative optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Ophthalmology*,

PURPOSE: To detect and quantify choroidal neovascularization (CNV) in patients with age-related macular degeneration (AMD) using optical coherence tomography (OCT) angiography. DESIGN: Observational, cross-sectional study. PARTICIPANTS: A total of 5 normal subjects and 5 subjects with neovascular AMD were included. METHODS: A total of 5 eyes with neovascular AMD and 5 normal age-matched controls were scanned by a high-speed (100 000 A-scans/seconds) 1050-nm wavelength swept-source OCT. The macular angiography scan covered a 3x3-mm area and comprised 200x200x8 A-scans acquired in 3.5 seconds. Flow was detected using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. Motion artifacts were removed by 3-dimensional (3D) orthogonal registration and merging of 4 scans. The 3D angiography was segmented into 3 layers: inner retina (to show retinal vasculature), outer retina

(to identify CNV), and choroid. En face maximum projection was used to obtain 2-dimensional angiograms from the 3 layers. The CNV area and flow index were computed from the en face OCT angiogram of the outer retinal layer. Flow (decorrelation) and structural data were combined in composite color angiograms for both en face and cross-sectional views. MAIN OUTCOME MEASUREMENTS: The CNV angiogram, CNV area, and CNV flow index. RESULTS: En face OCT angiograms of CNV showed sizes and locations that were confirmed by fluorescein angiography (FA). Optical coherence tomography angiography provided more distinct vascular network patterns that were less obscured by subretinal hemorrhage. The en face angiograms also showed areas of reduced choroidal flow adjacent to the CNV in all cases and significantly reduced retinal flow in 1 case. Cross-sectional angiograms were used to visualize CNV location relative to the retinal pigment epithelium and Bruch's layer and classify type I and type II CNV. A feeder vessel could be identified in 1 case. Higher flow indexes were associated with larger CNV and type II CNV. CONCLUSIONS: Optical coherence tomography angiography provides depth-resolved information and detailed images of CNV in neovascular AMD. Quantitative information regarding CNV flow and area can be obtained. Further studies are needed to assess the role of quantitative OCT angiography in the evaluation and treatment of neovascular AMD.

Kalpathy-Cramer, J., de Herrera, A. G., Demner-Fushman, D., Antani, S., Bedrick, S., & Muller, H. (2014). Evaluating performance of biomedical image retrieval systems-an overview of the medical image retrieval task at ImageCLEF 2004-2013. *Computerized Medical Imaging and Graphics : The Official Journal of the Computerized Medical Imaging Society*,
Medical image retrieval and classification have been extremely active research topics over the past 15 years. Within the ImageCLEF benchmark in medical image retrieval and classification, a standard test bed was created that allows researchers to compare their approaches and ideas on increasingly large and varied data sets including generated ground truth. This article describes the lessons learned in ten evaluation campaigns. A detailed analysis of the data also highlights the value of the resources created.

Kang, E., Wu, G., Ma, H., Li, Y., Tippner-Hedges, R., Tachibana, M., et al. (2014). Nuclear reprogramming by interphase cytoplasm of two-cell mouse embryos. *Nature*, *509*(7498), 101-

104.

Successful mammalian cloning using somatic cell nuclear transfer (SCNT) into unfertilized, metaphase II (MII)-arrested oocytes attests to the cytoplasmic presence of reprogramming factors capable of inducing totipotency in somatic cell nuclei. However, these poorly defined maternal factors presumably decline sharply after fertilization, as the cytoplasm of pronuclear-stage zygotes is reportedly inactive. Recent evidence suggests that zygotic cytoplasm, if maintained at metaphase, can also support derivation of embryonic stem (ES) cells after SCNT, albeit at low efficiency. This led to the conclusion that critical oocyte reprogramming factors present in the metaphase but not in the interphase cytoplasm are 'trapped' inside the nucleus during interphase and effectively removed during enucleation. Here we investigated the presence of reprogramming activity in the cytoplasm of interphase two-cell mouse embryos (I2C). First, the presence of candidate reprogramming factors was documented in both intact and enucleated metaphase and interphase zygotes and two-cell embryos. Consequently, enucleation did not provide a likely explanation for the inability of interphase cytoplasm to induce reprogramming. Second, when we carefully synchronized the cell cycle stage between the transplanted nucleus (ES cell, fetal fibroblast or terminally differentiated cumulus cell) and the recipient I2C cytoplasm, the reconstructed SCNT embryos developed into blastocysts and ES cells capable of contributing to traditional germline and tetraploid chimaeras. Last, direct transfer of cloned embryos, reconstructed with ES cell nuclei, into recipients resulted in live offspring. Thus, the cytoplasm of I2C supports efficient reprogramming, with cell cycle synchronization between the donor nucleus and recipient cytoplasm as the most critical parameter determining success. The ability to use interphase cytoplasm in SCNT could aid efforts to generate autologous human ES cells for regenerative applications, as donated or discarded embryos are more accessible than unfertilized MII oocytes.

Kelly, S. P., Jones, A., & Steelman, R. (2014). Case report: Pulmonary edema induced by breath holding in an adolescent patient. *AACN Advanced Critical Care*, *25*(2), 101-103.

Khan, K., Ismail, A. A., Abdel Rasoul, G., Bonner, M. R., Lasarev, M. R., Hendy, O., et al. (2014). Longitudinal assessment of chlorpyrifos exposure and self-reported neurological symptoms in

adolescent pesticide applicators. *BMJ Open*, *4*(3)

Objectives: Occupational exposure of organophosphorus pesticides, such as chlorpyrifos (CPF), in adolescents is of particular concern because of the potential vulnerability of the developing neurological system. The objectives of this study were to examine how neurological symptoms reported over the application season vary across time, whether these effects are reversible postapplication and if there are associations between CPF biomarkers and neurological symptoms in an adolescent study population. Setting: The longitudinal study was conducted in two agricultural districts of Menoufia Governorate, Egypt between April 2010 and January 2011. Participants: Male adolescent participants, including CPF applicators (n=57) and non-applicators (n=38), were recruited. Primary and secondary outcome measures: Self-reported data for 25 neurological symptoms were collected at 32 time points over the 8-month period before, during and after the application season. Additionally, urine and blood samples were collected to measure urine trichloro-2-pyridinol (TCPy), a CPF-specific biomarker and blood cholinesterase activity. Results: Applicators and non-applicators report the highest numbers of symptoms during the application season, followed by a reduction in symptoms after the application ended. Applicators reported a greater percentage of neurological symptoms, relative to baseline, than non-applicators after accounting for potential covariates. Among the applicators, cumulative TCPy was positively and significantly associated with the average percentage of symptoms (B=4.56, 95% CI 3.29 to 5.84; p<0.001). Significant associations (p=0.03-0.07) between the change in butyrylcholinesterase activity from the preapplication to the postapplication season and several domains of neurological symptoms were also found, even after adjusting for potential covariates. Conclusions: These observations demonstrate changes in the reporting of symptoms across the application season, showing an increase in symptom reporting during application and recovery following the end of pesticide application. These findings reinforce the growing concern regarding the neurotoxic health effects of CPF in adolescent applicators in developing countries and the need for developing and implementing intervention programmes.

Kiguchi, M., Leake, A., Switzer, G., Mitchell, E., Makaroun, M., & Chaer, R. A. (2014). Perceptions of society for vascular surgery members andurgery department chairs of the integrated 0 + 5 vascular surgery training paradigm. *Journal of Surgical Education*,

Introduction: As the first generation of integrated (0 + 5) vascular surgery (VS) residents enter the job market, this survey sought to understand how the surgical community perceives this training paradigm. Methods: An anonymous online survey was e-mailed to surgery chairpersons (n = 193) and Society for Vascular Surgery (SVS) members (n = 2193) in the United States/Canada with 26% (n = 38) and 14% (n = 309) response rates, respectively. Respondents were asked about their practice background, residency program, hiring patterns, and perceptions of the 0 + 5 training. Results: Response rates were 26% (n = 38) and 14% (n = 309) for surgery chairpersons and SVS members, respectively. SVS respondents were from academic (62%) and private (38%) practices and included staff surgeons (62%), program directors (15%), and division chiefs (22%). Only 33% had a 0 + 5 program, and 57% had a VS fellowship. Overall, 94% were likely to hire a new vascular surgeon in the next 5 years. In some categories, SVS respondents believed 0 + 5 residents would be less prepared than 5 + 2 residents. Only 32% thought that 0 + 5 residents have the same level of surgical maturity, and 36% thought that they have the same level of open operative skills as 5 + 2 trainees. Another 34% thought 0 + 5 residents will need additional fellowship training in open surgery. However, there was also a general perception from SVS respondents that 0 + 5 residents would be prepared for clinical practice (67%) and would have equal endovascular skills to 5 + 2 trainees (92%). The chairpersons had similar perceptions as SVS members. Both SVS members (88%) and chairpersons (86%) would consider interviewing a 0 + 5 graduate for faculty position; 83% and 72%, respectively, would consider hiring. Moreover, 93% of SVS respondents who currently have a 0 + 5 program and 86% of SVS respondents who do not would consider hiring a 0 + 5 graduate. Both SVS members (62%) and chairpersons (50%) believed the 0 + 5 paradigm is essential for the advancement of VS. Conclusions: Overall perceptions of 0 + 5 graduates were positive and indicated their likely acceptance into the VS workforce. Although there were some reservations regarding the 0 + 5 graduates' maturity level and open operative skills, the surgical community was willing to interview and hire these trainees for staff positions. Further follow-up will be required to evaluate their performance in clinical practice.

Kim, E. -., Kim, J. -., Chang, Y. -., Turcio-Ortega, D., & Tratnyek, P. G. (2014). Effects of metal ions on the reactivity and corrosion electrochemistry of Fe/FeS nanoparticles. *Environmental Science*

*and Technology*, *48*(7), 4002-4011.

Nano-zerovalent iron (nZVI) formed under sulfidic conditions results in a biphasic material (Fe/FeS) that reduces trichloroethene (TCE) more rapidly than nZVI associated only with iron oxides (Fe/FeO). Exposing Fe/FeS to dissolved metals (Pd2+, Cu2+, Ni2+, Co2+, and Mn2+) results in their sequestration by coprecipitation as dopants into FeS and FeO and/or by electroless precipitation as zerovalent metals that are hydrogenation catalysts. Using TCE reduction rates to probe the effect of metal amendments on the reactivity of Fe/FeS, it was found that Mn2+ and Cu2+ decreased TCE reduction rates, while Pd2+, Co2+, and Ni2+ increased them. Electrochemical characterization of metal-amended Fe/FeS showed that aging caused passivation by growth of FeO and FeS phases and poisoning of catalytic metal deposits by sulfide. Correlation of rate constants for TCE reduction (kobs) with electrochemical parameters (corrosion potentials and currents, Tafel slopes, and polarization resistance) and descriptors of hydrogen activation by metals (exchange current density for hydrogen reduction and enthalpy of solution into metals) showed the controlling process changed with aging. For fresh Fe/FeS, kobs was best described by the exchange current density for activation of hydrogen, whereas kobs for aged Fe/FeS correlated with electrochemical descriptors of electron transfer. © 2014 American Chemical Society.

Kiraly, L. N., McClave, S. A., Neel, D., Evans, D. C., Martindale, R. G., & Hurt, R. T. (2014). Physician nutrition education. *Nutrition in Clinical Practice : Official Publication of the American Society for Parenteral and Enteral Nutrition*,

Nutrition education for physicians in the United States is limited in scope, quality, and duration due to a variety of factors. As new data and quality improvement initiatives highlight the importance of nutrition and a generation of nutrition experts retire, there is a need for new physician educators and leaders in clinical nutrition. Traditional nutrition fellowships and increased didactic lecture time in school and postgraduate training are not feasible strategies to develop the next generation of physician nutrition specialists in the current environment. One strategy is the development of short immersion courses for advanced trainees and junior attendings. The most promising courses include a combination of close mentorship and adult learning techniques such as lectures, clinical experiences, literature review, curricular

development, research and writing, multidisciplinary interactions, and extensive group discussion. These courses also allow the opportunity for advanced discourse, development of long-term collaborative relationships, and continued longitudinal career development for alumni after the course ends. Despite these curricular developments, ultimately the field of nutrition will not mature until the American Board of Medical Specialties recognizes nutrition medicine with specialty board certification.

Kita, S., Yaeko, K., & Porter, S. E. (2014). Prevalence and risk factors of intimate partner violence among pregnant women in japan. *Health Care for Women International*, *35*(4), 442-457. Intimate partner violence (IPV) during pregnancy can result in adverse outcomes for both mothers and their infants. This cross-sectional study examined the prevalence and risk factors of IPV associated with abuse during pregnancy via a self-administered questionnaire completed by 302 healthy pregnant women. Demographic information was also collected from medical records to analyze risk factors for abuse. Of the 302 women, 48 (15.9%) were identified as experiencing IPV. The identified risk factors were age over 30, multipara, previous abortion experience, and male partner aged under 30. © 2014 Taylor & Francis.

Klein, E., & Bourdette, D. (2014). Authors respond. *Neurology: Clinical Practice*, *4*(1), 3.

Koehler, S. A., & Freeman, M. D. (2014). Forensic epidemiology: A method for investigating and quantifying specific causation. *Forensic Science, Medicine, and Pathology*, *10*(2), 217-222. The field of forensic epidemiology was initially introduced as a systematic approach to the investigation of acts of bioterrorism. In recent years, however, the applications of forensic epidemiology have expanded greatly, covering a wide range of medicolegal issues routinely encountered in both criminal and civil court settings. Forensic epidemiology provides a method of evaluating causation in groups and individuals based in the application of the Hill Criteria, with conclusions given in terms of relative or comparative risk, or as a Probability of Causation. The purpose of this paper is to give a brief overview of the methods and applications of forensic epidemiology. © 2013 Springer Science+Business Media New York.

Kudenchuk, P. J., Brown, S. P., Daya, M., Morrison, L. J., Grunau, B. E., Rea, T., et al. (2014). Resuscitation outcomes consortium-amiodarone, lidocaine or placebo study (ROC-ALPS): Rationale and methodology behind an out-of-hospital cardiac arrest antiarrhythmic drug trial. *American Heart Journal*,

Despite their wide use, whether antiarrhythmic drugs improve survival after out-of-hospital cardiac arrest (OHCA) is not known. The ROC-ALPS is evaluating the effectiveness of these drugs for OHCA due to shock-refractory ventricular fibrillation or pulseless ventricular tachycardia (VF/VT). Methods: ALPS will randomize 3,000 adults across North America with nontraumatic OHCA, persistent or recurring VF/VT after ≥1 shock, and established vascular access to receive up to 450 mg amiodarone, 180 mg lidocaine, or placebo in the field using a double-blind protocol, along with standard resuscitation measures. The designated target population is all eligible randomized recipients of any dose of ALPS drug whose initial OHCA rhythm was VF/VT. A safety analysis includes all randomized patients regardless of their eligibility, initial arrhythmia, or actual receipt of ALPS drug. The primary outcome of ALPS is survival to hospital discharge; a secondary outcome is functional survival at discharge assessed as a modified Rankin Scale score ≤3. Results: The principal aim of ALPS is to determine if survival is improved by amiodarone compared with placebo; secondary aim is to determine if survival is improved by lidocaine vs placebo and/or by amiodarone vs lidocaine. Prioritizing comparisons in this manner acknowledges where differences in outcome are most expected based on existing knowledge. Each aim also represents a clinically relevant comparison between treatments that is worth investigating. Conclusions: Results from ALPS will provide important information about the choice and value of antiarrhythmic therapies for VF/VT arrest with direct implications for resuscitation guidelines and clinical practice. © 2014 Mosby, Inc. All rights reserved.

Kumar, R., Matsumura, H., Lovell, S., Yao, H., Rodríguez, J. C., Battaile, K. P., et al. (2014). Replacing the axial ligand tyrosine 75 or its hydrogen bond partner histidine 83 minimally affects hemin acquisition by the hemophore HasAp from pseudomonas aeruginosa. *Biochemistry*, *53*(13), 2112-2125.

Hemophores from Pseudomonas aeruginosa (HasAp), Serratia marcescens (HasAsm), and Yersinia pestis (HasAyp) bind hemin between two loops. One of the loops harbors conserved axial

ligand Tyr75 (Y75 loop) in all three structures, whereas the second loop (H32 loop) contains axial ligand His32 in HasAp and HasAsm, but a noncoordinating Gln32 in HasA yp. Binding of hemin to the Y75 loop of HasAp or HasAsm causes a large rearrangement of the H32 loop that allows His32 coordination. The Q32 loop in apo-HasAyp is already in the closed conformation, such that binding of hemin to the conserved Y75 loop occurs with minimal structural rearrangement and without coordinative interaction with the Q32 loop. In this study, structural and spectroscopic investigations of the hemophore HasAp were conducted to probe (i) the role of the conserved Tyr75 loop in hemin binding and (ii) the proposed requirement of the His83-Tyr75 hydrogen bond to allow the coordination of hemin by Tyr75. High-resolution crystal structures of H83A holo-HasAp obtained at pH 6.5 (0.89 Å) and pH 5.4 (1.25 Å) show that Tyr75 remains coordinated to the heme iron, and that a water molecule can substitute for Nδ of His83 to interact with the O η atom of Tyr75, likely stabilizing the Tyr75-Fe interaction. Nuclear magnetic resonance spectroscopy revealed that in apo-Y75A and apo-H83A HasAp, the Y75 loop is disordered, and that disorder propagates to nearby elements of secondary structure, suggesting that His83 Nδ-Tyr75 Oη interaction is important to the organization of the Y75 loop in apo-HasA. Kinetic analysis of hemin loading conducted via stopped-flow UV-vis and rapid-freeze-quench resonance Raman shows that both mutants load hemin with biphasic kinetic parameters that are not significantly dissimilar from those previously observed for wild-type HasAp. When the structural and kinetic data are taken together, a tentative model emerges, which suggests that HasA hemophores utilize hydrophobic, π-π stacking, and van der Waals interactions to load hemin efficiently, while axial ligation likely functions to slow hemin release, thus allowing the hemophore to meet the challenge of capturing hemin under inhospitable conditions and delivering it selectively to its cognate receptor. 

Lammers, P. E., Shyr, Y., Li, C. I., Hutchison, A. S., Sandler, A., Carbone, D. P., et al. (2014). Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*, *9*(4), 559-562.

INTRODUCTION: To determine the time to progression (TTP), response rate (RR), and toxicity for North American patients with relapsed small-cell lung cancer (SCLC) treated with bendamustine

in the second- or third-line setting. METHODS: Patients with relapsed, histologically confirmed SCLC were eligible for enrollment on study. The study population included patients with both chemotherapy-sensitive and chemotherapy-resistant disease treated with up to two prior lines of chemotherapy. Patients were treated with 120 mg/m of bendamustine on days 1 and 2 of a 21-day cycle for up to six cycles. Primary end point was TTP; secondary end points included toxicity, RR, and overall survival. RESULTS: Fifty-nine patients were accrued, 50 patients met eligibility for enrollment. The median age of patients was 62, and 56% were men. Twenty-nine patients (58%) had chemotherapy-sensitive disease. Median TTP was 4.0 months (95% confidence interval [CI], 3.3-5.4), median overall survival was 4.8 months (95% CI, 3.8-6.3), and the RR was 26% (95% CI, 13.3%-39.5%). Patients with chemosensitive disease had a median TTP of 4.2 months (95% CI, 3.3-6.0) compared with 3.4 months (95% CI, 2.7-infinity) for chemotherapy-resistant disease. The RR was 33% (95% CI, 14.2%-51.8%) in patients with chemosensitive disease and 17% (95% CI, 0%-34.4%) in those with chemoresistant disease. The most common grade 3/4 adverse events were fatigue (20%), dyspnea (12%), and anemia (12%). CONCLUSION: Bendamustine has modest activity in relapsed SCLC similar to other agents evaluated in this patient population.

Li, F., Harmer, P., Liu, Y., Eckstrom, E., Fitzgerald, K., Stock, R., et al. (2014). A randomized controlled trial of patient-reported outcomes with tai chi exercise in parkinson's disease. *Movement Disorders*, *29*(4), 539-545.

A previous randomized, controlled trial of tai chi showed improvements in objectively measured balance and other motor-related outcomes in patients with Parkinson's disease. This study evaluated whether patient-reported outcomes could be improved through exercise interventions and whether improvements were associated with clinical outcomes and exercise adherence. In a secondary analysis of the tai chi trial, patient-reported and clinical outcomes and exercise adherence measures were compared between tai chi and resistance training and between tai chi and stretching exercise. Patient-reported outcome measures were perceptions of health-related benefits resulting from participation, assessed by the Parkinson's Disease Questionnaire (PDQ-8) and Vitality Plus Scale (VPS). Clinical outcome measures included motor symptoms, assessed by a modified Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) and a 50-

foot speed walk. Information on continuing exercise after the structured interventions were terminated was obtained at a 3-month postintervention follow-up. Tai chi participants reported significantly better improvement in the PDQ-8 (-5.77 points, P=0.014) than did resistance training participants and in PDQ-8 (-9.56 points, P<0.001) and VPS (2.80 points, P=0.003) than did stretching participants. For tai chi, patient-reported improvement in the PDQ-8 and VPS was significantly correlated with their clinical outcomes of UPDRS-ME and a 50-foot walk, but these correlations were not statistically different from those shown for resistance training or stretching. However, patient-reported outcomes from tai chi training were associated with greater probability of continued exercise behavior than were either clinical outcomes or patient-reported outcomes from resistance training or stretching. Tai chi improved patient-reported perceptions of health-related benefits, which were found to be associated with a greater probability of exercise adherence. The findings indicate the potential of patient perceptions to drive exercise behavior after structured exercise programs are completed and the value of strengthening such perceptions in any behavioral intervention. 

Li, G., Millard, S. P., Peskind, E. R., Zhang, J., Yu, C. E., Leverenz, J. B., et al. (2014). Cross-sectional and longitudinal relationships between cerebrospinal fluid biomarkers and cognitive function in people without cognitive impairment from across the adult life span. *JAMA Neurology*, IMPORTANCE Age-related cognitive decline among older individuals with normal cognition is a complex trait that potentially derives from processes of aging, inherited vulnerabilities, environmental factors, and common latent diseases that can progress to cause dementia, such as Alzheimer disease and vascular brain injury. OBJECTIVE To use cerebrospinal fluid (CSF) biomarkers to gain insight into this complex trait. DESIGN, SETTING, AND PARTICIPANTS Secondary analyses of an academic multicenter cross-sectional (n = 315) and longitudinal (n = 158) study of 5 neuropsychological tests (Immediate Recall, Delayed Recall, Trail Making Test Parts A and B, and Category Fluency) in cognitively normal individuals aged 21 to 100 years. MAIN OUTCOMES AND MEASURES To investigate the association of these cognitive function test results with age, sex, educational level, inheritance of the epsilon4 allele of the apolipoprotein E gene, and CSF concentrations of beta-amyloid 42 (Abeta42) and tau (biomarkers of Alzheimer

disease) as well as F2-isoprostanes (measures of free radical injury). RESULTS Age and educational level were broadly predictive of cross-sectional cognitive performance; of the genetic and CSF measures, only greater CSF F2-isoprostane concentration was significantly associated with poorer executive function (adjusted R2 </=0.31). Longitudinal measures of cognitive abilities, except Category Fluency, also were associated broadly with age; of the genetic and CSF measures, only lower baseline CSF Abeta42 concentration was associated with longitudinal measures of immediate and delayed recall (marginal R2 </=0.31). CONCLUSIONS AND RELEVANCE Our results suggest that age and educational level accounted for a substantial minority of variance in cross-sectional or longitudinal cognitive test performance in this large group of cognitively normal adults. Latent Alzheimer disease and other diseases that produce free radical injury, such as vascular brain injury, accounted for a small amount of variation in cognitive test performance across the adult human life span. Additional genetic and environmental factors likely contribute substantially to age-related cognitive decline.

Lindauer, A., & A Harvath, T. (2014). Pre-death grief in the context of dementia caregiving: A concept analysis. *Journal of Advanced Nursing*,

AIM: The aim of this study was to report on an analysis of the concept of pre-death grief in the context of dementia family caregiving. BACKGROUND: Research indicates that witnessing changes and losses in a family member with dementia can lead to pre-death grief. Pre-death grief is associated with depression, burden and maladaptive caregiver coping. However, the concept lacks a refined definition and blurs with similar constructs. DESIGN: Concept analysis using a hybrid of Penrod and Hupcey's principle-based concept analysis and Chin and Kramer's conceptualization of meaning. DATA SOURCES: 49 peer-reviewed papers (2000-2013) that addressed pre-death grief in dementia family caregivers were used for the principle-based analysis; two examples from the popular media were used for the analysis of conceptual meaning. METHODS: The scientific papers were examined for epistemological, linguistic, pragmatic and logical clarity. The two examples from the popular media were explored for conceptual meaning. RESULTS: Pre-death grief in the context of dementia caregiving is a meaningful concept found in the popular media. From a scholarly point of view, it is an emerging concept. A definition is offered to advance conceptual clarity. Discussion focuses on advancing

the concept into a situation-specific middle-range theory of pre-death grief in family caregiving. CONCLUSIONS: The concept of pre-death grief has salience for researchers and caregivers. This analysis lays the foundation for use of the concept in nursing research and practice across cultural, environmental and illness domains.

Link, J. M., & Hurlin, P. J. (2014). The activities of MYC, MNT and the MAX-interactome in lymphocyte proliferation and oncogenesis. *Biochimica Et Biophysica Acta,*

The MYC family of proteins plays essential roles in embryonic development and in oncogenesis. Efforts over the past 30years to define the transcriptional activities of MYC and how MYC functions to promote proliferation have produced evolving models of MYC function. One picture that has emerged of MYC and its partner protein MAX is of a transcription factor complex with a seemingly unique ability to stimulate the transcription of genes that are epigenetically poised for transcription and to amplify the transcription of actively transcribed genes. During lymphocyte activation, MYC is upregulated and stimulates a pro-proliferative program in part through the upregulation of a wide variety of metabolic effector genes that facilitate cell growth and cell cycle progression. MYC upregulation simultaneously sensitizes cells to apoptosis and activated lymphocytes and lymphoma cells have pro-survival attributes that allow MYC-driven proliferation to prevail. For example, the MAX-interacting protein MNT is upregulated in activated lymphocytes and was found to protect lymphocytes from MYC-dependent apoptosis. Here we review the activities of MYC, MNT and other MAX interacting proteins in the setting of T and B cell activation and oncogenesis. This article is part of a Special Issue entitled: Myc proteins in cell biology and pathology.

Liu, J., Ogden, A., Comery, T. A., Spiros, A., Roberts, P., & Geerts, H. (2014). Prediction of efficacy of vabicaserin, a 5-HT2C agonist, for the treatment of schizophrenia using a quantitative systems pharmacology model. *CPT: Pharmacometrics & Systems Pharmacology, 3*, e111.

A quantitative systems pharmacology model that combines in vitro/preclinical neurophysiology data, human imaging data, and patient disease information was used to blindly predict steady-state clinical efficacy of vabicaserin, a 5-HT2C full agonist, in monotherapy and, subsequently, to assess adjunctive therapy in schizophrenia. The model predicted a concentration-dependent

improvement of positive and negative syndrome scales (PANSS) in schizophrenia monotherapy with vabicaserin. At the exposures of 100 and 200 mg b.i.d., the predicted improvements on PANSS in virtual patient trials were 5.12 (2.20, 8.56) and 6.37 (2.27, 10.40) (mean (95% confidence interval)), respectively, which are comparable to the observed phase IIa results. At the current clinical exposure limit of vabicaserin, the model predicted an ~9-point PANSS improvement in monotherapy, and <4-point PANSS improvement adjunctive with various antipsychotics, suggesting limited clinical benefit of vabicaserin in schizophrenia treatment. In conclusion, the updated quantitative systems pharmacology model of PANSS informed the clinical development decision of vabicaserin in schizophrenia.

Longo, N., Harding, C. O., Burton, B. K., Grange, D. K., Vockley, J., Wasserstein, M., et al. (2014). Single-dose, subcutaneous recombinant phenylalanine ammonia lyase conjugated with polyethylene glycol in adult patients with phenylketonuria: An open-label, multicentre, phase 1 dose-escalation trial. *Lancet*,

BACKGROUND: Phenylketonuria is an inherited disease caused by impaired activity of phenylalanine hydroxylase, the enzyme that converts phenylalanine to tyrosine, leading to accumulation of phenylalanine and subsequent neurocognitive dysfunction. Phenylalanine ammonia lyase is a prokaryotic enzyme that converts phenylalanine to ammonia and trans-cinnamic acid. We aimed to assess the safety, tolerability, pharmacokinetic characteristics, and efficacy of recombinant Anabaena variabilis phenylalanine ammonia lyase (produced in Escherichia coli) conjugated with polyethylene glycol (rAvPAL-PEG) in reducing phenylalanine concentrations in adult patients with phenylketonuria. METHODS: In this open-label, phase 1, multicentre trial, single subcutaneous injections of rAvPAL-PEG were given in escalating doses (0.001, 0.003, 0.010, 0.030, and 0.100 mg/kg) to adults with phenylketonuria. Participants aged 18 years or older with blood phenylalanine concentrations of 600 mumol/L or higher were recruited from among patients attending metabolic disease clinics in the USA. The primary endpoints were safety and tolerability of rAvPAL-PEG. Secondary endpoints were the pharmacokinetic characteristics of the drug and its effect on concentrations of phenylalanine. Participants and investigators were not masked to assigned dose group. This study is registered with ClinicalTrials.gov, number NCT00925054. FINDINGS: 25 participants were recruited from

seven centres between May 6, 2008, and April 15, 2009, with five participants assigned to each escalating dose group. All participants were included in the safety population. The most frequently reported adverse events were injection-site reactions and dizziness, which were self-limited and without sequelae. Two participants had serious adverse reactions to intramuscular medroxyprogesterone acetate, a drug that contains polyethylene glycol as an excipient. Three of five participants given the highest dose of rAvPAL-PEG (0.100 mg/kg) developed a generalised skin rash. By the end of the study, all participants had developed antibodies against polyethylene glycol, and some against phenylalanine ammonia lyase as well. Drug concentrations peaked about 89-106 h after administration of the highest dose. Treatment seemed to be effective at reducing blood phenylalanine in all five participants who received the highest dose (mean reduction of 54.2% from baseline), with a nadir about 6 days after injection and an inverse correlation between drug and phenylalanine concentrations in plasma. Phenylalanine returned to near-baseline concentrations about 21 days after the injection. INTERPRETATION: Subcutaneous administration of rAvPAL-PEG in a single dose of up to 0.100 mg/kg was fairly safe and well tolerated in adult patients with phenylketonuria. At the highest dose tested, rAvPAL-PEG reduced blood phenylalanine concentrations. In view of the development of antibodies against polyethylene glycol (and in some cases against phenylalanine ammonia lyase), future studies are needed to assess the effect of repeat dosing. FUNDING: BioMarin Pharmaceutical.

Lopez, A. M., Kornegay, J., & Hendrickson, R. G. (2014). Serotonin toxicity associated with garcinia cambogia over-the-counter supplement. *Journal of Medical Toxicology : Official Journal of the American College of Medical Toxicology*,

Lovejoy, T. I., & Heckman, T. G. (2014). Telephone-administered motivational interviewing and behavioral skills training to reduce risky sexual behavior in HIV-positive late middle-age and older adults. *Cognitive and Behavioral Practice, 21*(2), 224-236.

By 2014, 50% of all persons living with HIV/AIDS in the U.S. will be 50. years of age or older. An estimated 13% to 30% of HIV-positive older adults continue to engage in risky sexual behaviors that risk HIV transmission. Project SAFER, a large pilot randomized controlled trial, evaluated telephone-administered motivational interviewing and behavioral skills training to reduce sexual

risk behavior in HIV-positive, urban-dwelling late middle-age and older adults. The intervention consists of 4 weekly integrated motivational interviewing and behavioral skills training sessions delivered by a mental health clinician over the telephone. This paper highlights study procedures and intervention outcomes. The primary focus, however, is a detailed description of the 4-session intervention with sample counselor-client dialogue that is thematically emblematic of topics addressed in the intervention. We conclude with lessons learned conducting telephone-administered motivational interviewing and behavioral skills training with HIV-positive late middle-age and older adults. © 2013.

Lovejoy, T. I., Heckman, T. G., Sikkema, K. J., Hansen, N. B., & Kochman, A. (2014). Changes in sexual behavior of HIV-infected older adults enrolled in a clinical trial of standalone group psychotherapies targeting depression. *AIDS and Behavior*,

By 2015, one-half of all HIV-positive persons in the U.S. will be 50-plus years of age, and as many as 30 % of older adults living with HIV/AIDS continue to engage in unprotected sexual intercourse. Contemporary positive prevention models often include mental health treatment as a key component of HIV prevention interventions. This secondary data analysis characterized longitudinal patterns of sexual behavior in HIV-positive older adults enrolled in a randomized controlled trial of group mental health interventions and assessed the efficacy of psychosocial treatments that targeted depression to reduce sexual risk behavior. Participants were 295 HIV-positive adults >/=50 years of age experiencing mild to severe depressive symptoms, randomized to one of three study conditions: a 12-session coping improvement group intervention, a 12-session interpersonal support group intervention, or individual therapy upon request. Approximately one-fifth of participants reported one or more occasions of unprotected anal or vaginal intercourse with HIV-negative sexual partners or persons of unknown HIV serostatus over the study period. Changes in sexual behavior did not vary by intervention condition, indicating that standalone treatments that target and reduce depression may be insufficient to reduce sexual risk behavior in depressed HIV-positive older adults.

Luk, L., Mace, J. C., Bhandarkar, N. D., & Sautter, N. B. (2014). Comparison of electrosurgical plasma coagulation and potassium-titanyl-phosphate laser photocoagulation for treatment of hereditary

hemorrhagic telangiectasia-related epistaxis. *International Forum of Allergy & Rhinology*, BACKGROUND: Potassium-titanyl-phosphate (KTP) laser photocoagulation is commonly used for treatment of hereditary hemorrhagic telangiectasia-related epistaxis (HHT-RE). Electrosurgical plasma coagulation (EPC), also known as coblation, has not been rigorously evaluated for HHT-RE. METHODS: Patients seeking treatment for HHT-RE between September 2010 and September 2012 were prospectively randomized (1:1) to KTP or EPC in a single blind prospective cohort study. Length of surgery and estimated blood loss (EBL) were recorded. Epistaxis severity scores (ESSs) and 10-cm visual analogue scale (VAS) scores for HHT-RE-related symptoms were administered at enrollment and at 3, 6, 12 months following surgery. Statistical analysis used Friedman's and Pearson's chi-square tests. RESULTS: Eleven HHT patients were prospectively enrolled and followed. Six patients underwent EPC treatment while 5 underwent KTP. Three patients in the KTP subgroup and 2 patients in the EPC subgroup requested additional surgical treatment within 12 months ($p > 0.999$). There were no significant differences in terms of EBL ($p = 0.126$) and length of surgery ($p = 0.429$) between treatment groups. Mean ESSs were not significantly different between groups at any follow-up point (KTP, $p = 0.896$; EPC, $p = 0.159$). Compared to KTP, mean ESSs were higher in the EPC subgroup at baseline and lower at all other time points. Mean nasal obstruction VAS scores were significantly lower in the EPC subgroup at all follow-up points. CONCLUSION: EPC is a viable alternative to KTP laser photocoagulation for epistaxis control in patients with HHT. Subjectively, patients experience less nasal obstruction following EPC as compared to KTP treatment. A multicentered, well-powered study is warranted to better determine treatment outcomes.

Lurker, P. A., Berman, F., Clapp, R. W., & Stellman, J. (2014). Response to commentary: Post-vietnam military herbicide exposures in UC-123 agent orange spray aircraft. *Environmental Research*, *131C*, 215-216.

Lyons, K. S., Lee, C. S., Bennett, J. A., Nail, L. M., Fromme, E., Hiatt, S. O., et al. (2014). Symptom incongruence trajectories in lung cancer dyads. *Journal of Pain and Symptom Management*, CONTEXT: There is little known about the pattern of change in patient-family member symptom incongruence across the lung cancer trajectory. OBJECTIVES: This study examined trajectories of

patient-family member incongruence in perceptions of patient physical function, pain severity, fatigue, and dyspnea in lung cancer dyads and explored the association with family member grief post-patient death. METHODS: Lung cancer patients and their family members providing care (N=109 dyads) rated patient symptoms and physical function five times over 12 months. Symptom incongruence trajectories were analyzed using multilevel modeling (MLM). RESULTS: Patient-family member incongruence did not significantly change over time, on average, except in the case of patient physical function where incongruence significantly declined. There was significant variability around trajectories of incongruence for all symptoms except fatigue. Exploratory analysis on a sub-sample of 22 bereaved family members found incongruence regarding patient fatigue was associated with family member grief two months post-patient death. CONCLUSION: Findings suggest the importance of modeling symptom incongruence over time and taking a dyadic approach to the illness context to identify interventions that promote adjustment and quality of life for both patient and family member.

Ma, D. H. -., Yeh, L. -., Chen, H. -., Chang, A. M., Ho, Y. -., Chang, S. H. L., et al. (2014). Epithelial phenotype in total sclerocornea. *Molecular Vision*, *20*, 468-479.

Purpose: To understand whether the epithelial phenotype in total sclerocornea is corneal or conjunctival in origin. Methods: Four cases of total sclerocornea (male:female = 1:3; mean age = 5.4±4.3; 1-11 years old) who received penetrating keratoplasty (PKP) at our hospital between 2008 and 2011 were included. Corneal buttons obtained during PKP were used for transmission electron microscopy (TEM) as well as immunoconfocal microscopy for cytokeratins 3, 12, and 13, goblet cell mucin MUC5AC, connexin 43, stem cell markers p63 and ABCG2, laminin-5, and fibronectin. Results: After a mean follow-up period of 38.8±14.0 (12-54) months, the grafts remained clear in half of the patients. TEM examination revealed a markedly attenuated Bowman's layer in the scleralized corneas, with irregular and variably thinned collagen lamellar layers, and disorganization and random distribution of collagen fibrils, which were much larger in diameter compared with a normal cornea. Immunoconfocal microscopy showed that keratin 3 was expressed in all four patients, while p63, ABCG2, and MUC5AC were all absent. Cornea-specific keratin 12 was universally expressed in Patients 1 to 3, while mucosa (including conjunctiva)-specific keratin 13 was negative in these patients. Interestingly, keratin 12 and 13

were expressed in Patient 4 in a mutually exclusive manner. Linear expression of laminin-5 in the basement membrane zone and similar expression of fibronectin were observed. Conclusions: The epithelia in total sclerocornea are essentially corneal in phenotype, but in the event of massive corneal angiogenesis, invasion by the conjunctival epithelium is possible. © 2014 Molecular Vision.

Macey, T. A., Bobeck, E. N., Suchland, K. L., Morgan, M. M., & Ingram, S. L. (2014). Change in functional selectivity of morphine with the development of antinociceptive tolerance. *British Journal of Pharmacology*,

BACKGROUND: Opioids, such as morphine, are the most effective treatment for pain but their efficacy is diminished with the development of tolerance following repeated administration. Recently, we found that morphine activates extracellular signal-related kinase 1/2 (ERK) in opioid tolerant but not in naive rats suggesting that morphine activation of mu opioid receptors is altered following repeated morphine administration. The current studies tested the hypothesis that mu opioid receptor activation of ERK in the ventrolateral periaqueductal gray (vlPAG) is dependent on dynamin, a protein implicated in receptor endocytosis. EXPERIMENTAL APPROACH: Rats were made tolerant to repeated microinjections of morphine into the vlPAG. The effects of dynamin on ERK activation and antinociception were assessed by microinjecting myristoylated dominant negative dynamin peptide (Dyn-DN) or a scrambled control peptide (Dyn-scr) into the vlPAG. Microinjection of a fluorescent dermorphin analog (DERM-A594) into the vlPAG was used to monitor mu opioid receptor internalization. KEY RESULTS: Morphine did not activate ERK and Dyn-DN administration had no effect on morphine-induced antinociception in saline-pretreated rats. In contrast, morphine induced ERK activation in morphine-pretreated rats that was blocked by Dyn-DN administration. Dyn-DN also inhibited morphine antinociception. Finally, morphine reduced DERM-A594 internalization only in morphine tolerant rats indicating that mu opioid receptors were internalized and unavailable to bind DERM-A594. CONCLUSIONS: Repeated morphine administration increases mu opioid receptor activation of ERK signaling via a dynamin-dependent mechanism. These results demonstrate that the balance of agonist signaling to G-protein and dynamin-dependent pathways is altered, effectively changing the functional selectivity of the agonist-receptor complex.

Madry, H., Rey-Rico, A., Venkatesan, J. K., Johnstone, B., & Cucchiarini, M. (2014). Transforming growth factor beta-releasing scaffolds for cartilage tissue engineering. *Tissue Engineering - Part B: Reviews, 20*(2), 106-125.

The maintenance of a critical threshold concentration of transforming growth factor beta (TGF-β) for a given period of time is crucial for the onset and maintenance of chondrogenesis. Thus, the development of scaffolds that provide temporal and/or spatial control of TGF-β bioavailability has appeal as a mechanism to induce the chondrogenesis of stem cells in vitro and in vivo for articular cartilage repair. In the past decade, many types of scaffolds have been designed to advance this goal: hydrogels based on polysaccharides, hyaluronic acid, and alginate; protein-based hydrogels such as fibrin, gelatin, and collagens; biopolymeric gels and synthetic polymers; and solid and hybrid composite (hydrogel/solid) scaffolds. In this study, we review the progress in developing strategies to deliver TGF-β from scaffolds with the aim of enhancing chondrogenesis. In the future, such scaffolds could prove critical for tissue engineering cartilage, both in vitro and in vivo. © Mary Ann Liebert, Inc.

Maheshwari, A., Schelonka, R. L., Dimmitt, R. A., Carlo, W. A., Munoz-Hernandez, B., Das, A., et al. (2014). Cytokines associated with necrotizing enterocolitis in extremely-low-birth-weight infants. *Pediatric Research*,

Background:The goal was to identify cytokines associated with necrotizing enterocolitis (NEC). Based on our earlier reports of decreased tissue expression of transforming growth factor (TGF)-beta, we hypothesized that infants with NEC also have low blood TGF-beta levels. We further hypothesized that because fetal inflammation increases the risk of NEC, infants who develop NEC have elevated blood cytokine levels in early neonatal period.Methods:Data on 104 extremely-low-birth-weight infants with NEC and 893 without NEC from 17 centers were analyzed. Clinical information was correlated with blood cytokine levels on postnatal day 1 (D1), D3, D7, D14, and D21.Results:Male gender, non-Caucasian/non-African American ethnicity, sepsis, lower blood TGF-beta and interleukin (IL)-2 levels, and higher IL-8 levels were associated with NEC. The NEC group had lower TGF-beta levels than controls since D1. The diagnosis of NEC was associated with elevated IL-1beta, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1/CC-motif ligand-2, macrophage inflammatory protein-1beta/CC-motif ligand-3, and C-reactive

protein.Conclusion:Clinical characteristics, such as gender and ethnicity, and low blood TGF-beta levels are associated with higher risk of NEC. Infants who developed NEC did not start with high blood levels of inflammatory cytokines, but these rose mainly after the onset of NEC.Pediatric Research (2014); doi:10.1038/pr.2014.48.

Markiewicz, M. R., Verschueren, D., & Assael, L. A. (2010). Chromosome 4q deletion syndrome: Craniofacial characteristics associated with monosomy of the long arm of chromosome 4q. *The Cleft Palate-Craniofacial Journal : Official Publication of the American Cleft Palate-Craniofacial Association*, *47*(5), 518-522.

Chromosome 4q deletion syndrome is a monosomy that comprises all interstitial and terminal deletions of the long arm of chromosome 4. It results in a variety of phenotypes characterized by various craniofacial and bodily abnormalities. The purpose of this study is to report a case of 4q deletion syndrome and describe its clinical manifestations, with particular attention to the craniofacial presentation and subsequent management of the syndrome, as well as its associated micrognathia and airway complications. Among treatment options, the investigators chose bilateral distraction osteogenesis of the mandible in order to increase the subject's posterior airway space. At follow-up, the subject was able to ventilate without any adjuncts or mechanical ventilation assistance.

Marshall, N. E., Guild, C., Cheng, Y. W., Caughey, A. B., & Halloran, D. R. (2014). The effect of maternal body mass index on perinatal outcomes in women with diabetes. *American Journal of Perinatology*, *31*(3), 249-256.

Objective To determine the effect of increasing maternal obesity, including superobesity (body mass index [BMI] ≥ 50 kg/m2), on perinatal outcomes in women with diabetes. Study Design Retrospective cohort study of birth records for all live-born nonanomalous singleton infants ≥ 37 weeks' gestation born to Missouri residents with diabetes from 2000 to 2006. Women with either pregestational or gestational diabetes were included. Results There were 14,595 births to women with diabetes meeting study criteria, including 7,082 women with a BMI > 30 kg/m2 (48.5%). Compared with normal-weight women with diabetes, increasing BMI category, especially superobesity, was associated with a significantly increased risk for preeclampsia (adjusted

relative risk [aRR] 3.6, 95% confidence interval [CI] 2.5, 5.2) and macrosomia (aRR 3.0, 95% CI 1.8, 5.40). The majority of nulliparous obese women with diabetes delivered via cesarean including 50.5% of obese, 61.4% of morbidly obese, and 69.8% of superobese women. The incidence of primary elective cesarean among nulliparous women with diabetes increased significantly with increasing maternal BMI with over 33% of morbidly obese and 39% of superobese women with diabetes delivering electively by cesarean. Conclusion Increasing maternal obesity in women with diabetes is significantly associated with higher risks of perinatal complications, especially cesarean delivery. Copyright 2014 by Thieme Medical.

Martin, J. M., Gillingham, M. B., & Harding, C. O. (2014). Use of propofol for short duration procedures in children with long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) or trifunctional protein (TFP) deficiencies. *Molecular Genetics and Metabolism*,

The medication propofol, commonly used for anesthesia, has been avoided in patients with mitochondrial fatty acid oxidation disorders (FAODs) due to concerns that it contains long-chain fatty acids (LCFAs), and because of reports of severe side effects in some critically ill patients receiving high-dose propofol infusions that mimic some of the symptoms regularly found in FAOD patients. In this secondary analysis, we examined the outcomes of 8 children with long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) deficiency or trifunctional protein (TFP) deficiency who were repeatedly sedated for an electroretinogram (ERG) as part of a longitudinal study of the progression of chorioretinopathy commonly found in this population. A total of 39 sedated ERG procedures were completed using propofol for sedation. The propofol dosing, estimated total energy needs of the subject, and inpatient dietary intake recording were completed in 32 of these procedures. The LCFAs in the propofol provided approximately 1.0% of the average total daily energy needs. The sedation with propofol resulted in no adverse side effects and was safely used in this short duration procedure. 

Martínez-Salamanca, J. I., Linares, E., González, J., Bertini, R., Carballido, J. A., Chromecki, T., et al. (2014). Lessons learned from the international renal cell carcinoma-venous thrombus consortium (IRCC-VTC). *Current Urology Reports, 15*(5)

Renal cell carcinoma (RCC) extension into the renal vein or the inferior vena cava occurs in 4 %-

10 % of all kidney cancer cases. This entity shows a wide range of different clinical and surgical scenarios, making natural history and oncological outcomes variable and poorly characterized. Infrequency and variability make it necessary to share the experience from different institutions to properly analyze surgical outcomes in this setting. The International Renal Cell Carcinoma-Venous Tumor Thrombus Consortium was created to answer the questions generated by competing results from different retrospective studies in RCC with venous extension on current controversial topics. The aim of this article is to summarize the experience gained from the analysis of the world's largest cohort of patients in this unique setting to date. 

Matafonov, A., Leung, P. Y., Gailani, A. E., Grach, S. L., Puy, C., Cheng, Q., et al. (2014). Factor XII inhibition reduces thrombus formation in a primate thrombosis model. *Blood*, *123*(11), 1739-1746.

The plasma zymogens factor XII (fXII) and factor XI (fXI) contribute to thrombosis in a variety of mouse models. These proteins serve a limited role in hemostasis, suggesting that antithrombotic therapies targeting them may be associated with low bleeding risks. Although there is substantial epidemiologic evidence supporting a role for fXI in human thrombosis, the situation is not as clear for fXII. We generated monoclonal antibodies (9A2and15H8) against the human fXII heavy chain that interfere with fXII conversion to the protease factor XIIa (fXIIa). The anti-fXII antibodies were tested in models in which anti-fXI antibodies are known to have antithrombotic effects. Both anti-fXII antibodies reduced fibrin formation in human blood perfused through collagen-coated tubes. fXII-deficient mice are resistant to ferric chloride-induced arterial thrombosis, and this resistance can be reversed by infusion of human fXII. 9A2 partially blocks, and 15H8 completely blocks, the prothrombotic effect of fXII in this model. 15H8 prolonged the activated partial thromboplastin time of baboon and human plasmas. 15H8 reduced fibrin formation in collagen-coated vascular grafts inserted into arteriovenous shunts in baboons, and reduced fibrin and platelet accumulation downstream of the graft. These findings support a role for fXII in thrombus formation in primates. 

McCullough, B. J., Deyo, R. A., & Jarvik, J. G. (2014). In reply. *JAMA Internal Medicine, 174*(4), 642-643.

McCullough, B. J., Deyo, R. A., & Jarvik, J. G. (2014). Treatment of osteoporotic vertebral fractures-reply. *JAMA Internal Medicine, 174*(4), 642-643.

McEvoy, C. T., Jain, L., Schmidt, B., Abman, S., Bancalari, E., & Aschner, J. L. (2014). Bronchopulmonary dysplasia: NHLBI workshop on the primary prevention of chronic lung diseases. *Annals of the American Thoracic Society, 11 Suppl 3*, S146-53.
Bronchopulmonary dysplasia (BPD) is the most common complication of extreme preterm birth. Infants who develop BPD manifest aberrant or arrested pulmonary development and can experience lifelong alterations in cardiopulmonary function. Despite decades of promising research, primary prevention of BPD has proven elusive. This workshop report identifies current barriers to the conduct of primary prevention studies for BPD and causal pathways implicated in BPD pathogenesis. Throughout, we highlight promising areas for research to improve understanding of normal and aberrant lung development, distinguish BPD endotypes, and ascertain biomarkers for more targeted therapeutic approaches to prevention. We conclude with research recommendations and priorities to accelerate discovery and promote lung health in infants born preterm.

McKeown, N., Vetter, R. S., & Hendrickson, R. G. (2014). Verified spider bites in oregon (USA) with the intent to assess hobo spider venom toxicity. *Toxicon : Official Journal of the International Society on Toxinology, 84C*, 51-55.
This study compiled 33 verified spider bites from the state of Oregon (USA). The initial goal was to amass a series of bites by the hobo spider to assess whether it possesses toxic venom, a supposition which is currently in a contested state. None of the 33 bites from several spider species developed significant medical symptoms nor did dermonecrosis occur. The most common biters were the yellow sac spider, Cheiracanthium mildei (N = 10) and orb-weavers of the genus Araneus (N = 6). There were 10 bites from three genera of funnel web spiders of the family Agelenidae including one hobo spider bite and one from the congeneric giant house spider which is readily confused as a hobo spider. The hobo spider bite resulted in pain, redness, twitching in

the calf muscle and resolved in 12 h. Also generated from this study were possibly the first records of bites from spiders of the genera Callobius (Amaurobiidae) and Antrodiaetus (Antrodiaetidae), both with minor manifestations.

Mehra, S., Tuttle, R. M., Bergman, D., Bernet, V., Brett, E., Cobin, R., et al. (2014). Improving the quality of thyroid cancer care: How does the thyroid cancer care collaborative cross the institute of medicine's quality chasm? *Thyroid, 24*(4), 615-624.

Background: The current systems of healthcare delivery in the United States suffer from problems that often leave patients with inadequate quality of care. In their report entitled "Crossing the Quality Chasm," the Institute of Medicine (IOM) identified reasons for poor and/or inconsistent quality of healthcare delivery and provided recommendations to improve it. The purpose of this review is to describe features of an innovative web-based program called the Thyroid Cancer Care Collaborative (TCCC) and see how it addresses IOM recommendations to improve the quality of healthcare delivery. Summary: The TCCC addresses the three actionable IOM recommendations directed at healthcare organizations and clinicians to redesign the care process. It does so by exploiting information technology (IT) in ways suggested by the IOM, and it fits within a set of 10 rules provided by the IOM. Some features of the TCCC include: (i) automated disease staging based on three validated scoring systems; (ii) highly illustrated educational videos on all aspects of thyroid cancer care; (iii) personalized clinical decision-making modules for clinicians and physicians; (iv) portability of data to share among treating physicians; (v) virtual tumor boards, "ask the expert," and frequently asked questions modules; (vi) physician workflow integration; and (vii) data for comprehensive analysis to answer difficult questions in thyroid cancer management. Conclusion: The TCCC has the potential to improve thyroid cancer care delivery and offers several benefits to patients, clinicians, and researchers. The TCCC is a valuable example of how IOM initiatives can improve the healthcare system. © 2014, Mary Ann Liebert, Inc. 2014.

Mehta, A., & Ibsen, L. M. (2013). Neurologic complications and neurodevelopmental outcome with extracorporeal life support. *World Journal of Critical Care Medicine, 2*(4), 40-47.

Extracorporeal life support is used to support patients of all ages with refractory cardiac and/or

respiratory failure. Extracorporeal membrane oxygenation (ECMO) has been used to rescue patients whose predicted mortality would have otherwise been high. It is associated with acute central nervous system (CNS) complications and with long- term neurologic morbidity. Many patients treated with ECMO have acute neurologic complications, including seizures, hemorrhage, infarction, and brain death. Various pre-ECMO and ECMO factors have been found to be associated with neurologic injury, including acidosis, renal failure, cardiopulmonary resuscitation, and modality of ECMO used. The risk of neurologic complication appears to vary by age of the patient, with neonates appearing to have the highest risk of acute central nervous system complications. Acute CNS injuries are associated with increased risk of death in a patient who has received ECMO support. ECMO is increasingly used during cardiopulmonary resuscitation when return of spontaneous circulation is not achieved rapidly and outcomes may be good in select populations. Economic analyses have shown that neonatal and adult respiratory ECMO are cost effective. There have been several intriguing reports of active physical rehabilitation of patients during ECMO support that is well tolerated and may improve recovery. Although there is evidence that some patients supported with ECMO appear to have very good outcomes, there is limited understanding of the long-term impact of ECMO on quality of life and long-term cognitive and physical functioning for many groups, especially the cardiac and pediatric populations. This deserves further study.

Miranda-Dominguez, O., Mills, B. D., Grayson, D., Woodall, A., Grant, K. A., Kroenke, C. D., et al. (2014). Bridging the gap between the human and macaque connectome: A quantitative comparison of global interspecies structure-function relationships and network topology. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(16), 5552-5563.

Resting state functional connectivity MRI (rs-fcMRI) may provide a powerful and noninvasive "bridge" for comparing brain function between patients and experimental animal models; however, the relationship between human and macaque rs-fcMRI remains poorly understood. Here, using a novel surface deformation process for species comparisons in the same anatomical space (Van Essen, 2004, 2005), we found high correspondence, but also unique hub topology, between human and macaque functional connectomes. The global functional connectivity match

between species was moderate to strong (r = 0.41) and increased when considering the top 15% strongest connections (r = 0.54). Analysis of the match between functional connectivity and the underlying anatomical connectivity, derived from a previous retrograde tracer study done in macaques (Markov et al., 2012), showed impressive structure-function correspondence in both the macaque and human. When examining the strongest structural connections, we found a 70-80% match between structural and functional connectivity matrices in both species. Finally, we compare species on two widely used metrics for studying hub topology: degree and betweenness centrality. The data showed topological agreement across the species, with nodes of the posterior cingulate showing high degree and betweenness centrality. In contrast, nodes in medial frontal and parietal cortices were identified as having high degree and betweenness in the human as opposed to the macaque. Our results provide: (1) a thorough examination and validation for a surface-based interspecies deformation process, (2) a strong theoretical foundation for making interspecies comparisons of rs-fcMRI, and (3) a unique look at topological distinctions between the species.

Mitchell, J. E., King, W. C., Chen, J. -., Devlin, M. J., Flum, D., Garcia, L., et al. (2014). Course of depressive symptoms and treatment in the longitudinal assessment of bariatric surgery (LABS-2) study. *Obesity*,

Objective: To examine changes in depressive symptoms and treatment in the first 3 years following bariatric surgery. Methods: The longitudinal assessment of bariatric surgery-2 (LABS-2) is an observational cohort study of adults (n=2,458) who underwent a bariatric surgical procedure at 1 of 10 US hospitals between 2006 and 2009. This study includes 2,148 participants who completed the Beck depression inventory (BDI) at baseline and≥one follow-up visit in years 1-3. Results: At baseline, 40.4% self-reported treatment for depression. At least mild depressive symptoms (BDI score≥10) were reported by 28.3%; moderate (BDI score 19-29) and severe (BDI score ≥30) symptoms were uncommon (4.2 and 0.5%, respectively). Mild-to-severe depressive symptoms independently increased the odds (OR=1.75; P=0.03) of a major adverse event within 30 days of surgery. Compared with baseline, symptom severity was significantly lower at all follow-up time points (e.g., mild-to-severe symptomatology was 8.9%, 6 months; 8.4%, 1year; 12.2%, 2 years; 15.6%, 3 years; ps<0.001), but increased between 1 and 3 years

postoperatively (P<0.01). Change in depressive symptoms was significantly related to change in body mass index (r=0.42; P<0001). Conclusion: Bariatric surgery has a positive impact on depressive features. However, data suggest some deterioration in improvement after the first postoperative year. LABS-2, #NCT00465829, http://www.clinicaltrials.gov/ct2/show/NCT00465829. © 2014 The Obesity Society.

Modic, M. B., & Schoessler, M. (2013). Tanner's model of clinical judgment, part 2. *Journal for Nurses in Professional Development*, *29*(6), 335-337.

Modic, M. B., & Schoessler, M. (2014). Developing skills in interpretation. *Journal for Nurses in Professional Development*, *30*(1), 49-51.

Moore, J. P., Patel, P. A., Shannon, K. M., Albers, E. L., Salerno, J. C., Stein, M. A., et al. (2014). Predictors of myocardial recovery in pediatric tachycardia-induced cardiomyopathy. *Heart Rhythm : The Official Journal of the Heart Rhythm Society*,

BACKGROUND: Tachycardia-induced cardiomyopathy (TIC) carries significant risk of morbidity and mortality, although full recovery is possible. Little is known about the myocardial recovery pattern. OBJECTIVE: To determine the time course and predictors of myocardial recovery in pediatric TIC. METHODS: An international multicenter study of pediatric TIC was conducted. Children /=2) were included. Children with congenital heart disease or suspected primary cardiomyopathy (CM) were excluded. Primary endpoints were time to LV systolic functional recovery (LVEF>55%) and normal LV size (LVEDD z-score<2). RESULTS: Eighty-one children from 17 centers met inclusion criteria: median age 4.0 years (range 0.0-17.5); baseline LVEF 28% (IQR 19-39). The most common arrhythmias were EAT (59%), PJRT (23%), and VT (7%). Thirteen required ECMO (n=11) or VAD (n=2) support. Median time to recovery was 51 days for LVEF and 71 days for LVEDD. Two (4%) underwent heart transplantation and 1 died (1%). Multivariate predictors of LV systolic functional recovery were age (HR, 0.61; p=0.040), standardized tachycardia rate (HR, 1.16; p=0.015) and mechanical circulatory support (HR, 2.61; p=0.044) when adjusted for baseline LVEF. For normalization of LV size, only baseline LVEDD (HR, 0.86; p=0.008) was predictive. CONCLUSION: Pediatric TIC resolves in a predictable fashion. Factors associated with faster recovery include younger age, higher presenting heart

rate, use of mechanical circulatory support, and higher LVEF, while only smaller baseline LV size predicts reverse remodeling. This knowledge may be useful for clinical evaluation and follow-up of affected children.

Morasco, B. J., O'Neil, M. E., Duckart, J. P., & Ganzini, L. (2014). Comparison of health service use among veterans with methamphetamine versus alcohol use disorders. *Journal of Addiction Medicine, 8*(1), 47-52.

Objectives: Methamphetamine use disorders (MUD) are associated with severe health effects and psychiatric comorbidities, but little is known about the health care utilization of patients with MUD. The goal of this study was to describe health service use among veterans withMUDrelative to a group of veterans with an alcohol use disorder (AUD). Methods: Using Veterans Affairs (VA) administrative data, we identified 718 patients who were diagnosed with MUD and had confirmatory drug testing. Data were compared with those of 744 patients who had diagnoses of an AUD also with confirmatory testing. We examined diagnoses and medical utilization for 5 years after their index date. Results: Patients with MUD and laboratory-confirmed recent use were younger and more likely to be diagnosed with a mood disorder, posttraumatic stress disorder, and a psychotic-spectrum disorder (all P values < 0.05). After statistical controls, patients with MUD were more likely to have an inpatient hospitalization (80% vs 70%, odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.4-2.3), discharge from an inpatient admission against medical advice (23.4% vs 8.3%, OR = 2.6, 95% CI = 1.9-3.7), receive care at 3 or more VA medical centers (13.1% vs 5.4%, OR = 2.3, 95% CI = 1.5-3.5), have a behavioral flag in the medical record (5.6% vs 1.1%, OR = 4.6, 95% CI=2.1-10.6), and have more total missed appointments in the 5-year study period (M = 33.1 vs M = 23.5, P < 0.001). Conclusions: Among veterans with substance use disorders, those with MUD and laboratory-confirmed recent use have additional behavioral, health care utilization, and psychiatric characteristics that need to be considered in developing programs of care. 

Morris, C. D., McCracken, K., Samuels, M., & Orwoll, E. (2014). Creating an institutional resource for research education and career development: A novel model from oregon clinical and translational research institute. *Clinical and Translational Science,*

Moschak, T. M., & Mitchell, S. H. (2014). Partial inactivation of nucleus accumbens core decreases delay discounting in rats without affecting sensitivity to delay or magnitude. *Behavioural Brain Research*,

Increased preference for smaller, sooner rewards (delay discounting) is associated with several behavioral disorders, including ADHD and substance use disorders. However, delay discounting is a complex cognitive process and the relationship is unclear between the pathophysiology of the disorders and the component processes underlying delay discounting, including sensitivity to reinforcer delay and sensitivity to reinforcer magnitude. To investigate these processes, male Long Evans rats were trained in one of three tasks measuring sensitivity to delay, sensitivity to magnitude, or both (typical delay discounting task). After learning the task, animals were implanted with bilateral cannulae into either the nucleus accumbens core (AcbC) or the lateral orbitofrontal cortex (lOFC), both of which have been implicated in delay discounting. Upon recovering from the surgery, a baclofen/muscimol cocktail was infused to temporarily inactivate each of these two regions and task performance was assessed. Unlike previous studies showing that lesions of the AcbC increased delay discounting, partial inactivation of the AcbC decreased delay discounting, although it had no effects on the tasks independently assessing either sensitivity to delay or magnitude. The effects of AcbC inactivation were larger in animals that had low levels of delay discounting at baseline. Inactivation of the lOFC had no effects on behavior in any task. These findings suggest that the AcbC may act to promote impulsive choice in individuals with low impulsivity. Furthermore, the data suggest that the AcbC is able to modulate delay and magnitude sensitivity together, but not either of the two in isolation.

Motahari, S. M. A., Vedala, K., Goryawala, M., Cabrerizo, M., Yaylali, I., & Adjouadi, M. (2013). A somatosensory evoked potential monitoring algorithm using time frequency filtering. *2013 6th International IEEE EMBS Conference on Neural Engineering, NER 2013*, San Diego, CA. pp. 351-354.

A new method of detecting somatosensory evoked potentials (SSEP) is proposed using a time-frequency based windowing to enhance the signal to noise ratio (SNR) of the recorded SSEP signals. A sequential computation of maxima and minima was then used to find the location of characteristic positive and negative peaks of the SSEP. The algorithm rejects trials with high peak

value as they are corrupted with noise. The performance of the proposed algorithm was observed to be within acceptable clinical margins even with the use of only 30 consecutive trials at a time, thus proving to be very efficient for intraoperative neurophysiological monitoring during surgical procedures. 

Nabavizadeh, N., Zhang, J., Elliott, D. A., Tanyi, J. A., Thomas, C. R.,Jr, Fuss, M., et al. (2014). Electromagnetic navigational bronchoscopy-guided fiducial markers for lung stereotactic body radiation therapy: Analysis of safety, feasibility, and interfraction stability. *Journal of Bronchology & Interventional Pulmonology*, *21*(2), 123-130.

BACKGROUND: Embolization coils as fiducial markers for pulmonary stereotactic body radiation therapy (SBRT) are perceived to be the optimal marker type, given their ability to conform and anchor within the small airways. The aim of our study was to assess retention, placement, migration, feasibility, and safety of electromagnetic navigational bronchoscopy (ENB)-guided embolization coil markers throughout courses of SBRT. METHODS: Thirty-one patients with 34 nodules underwent ENB-guided fiducial placement of several 4 mm fibered platinum embolization coils before SBRT. Patient and nodule positioning was confirmed with daily pretreatment cone-beam computed tomography (CBCT). Fiducial positional characteristics were analyzed utilizing radiation treatment-planning software comparing the simulation CT with daily CBCTs. RESULTS: Of 105 fiducials placed, 103 were identifiable on simulation CT (retention rate: 98.1%). Incidence of asymptomatic pneumothoraces was 6%. One patient experienced hemoptysis requiring hospitalization. Eighty-six percent of fiducials were placed within 1 cm of the nodule, with 52% of fiducials placed directly on the nodule surface. Throughout a 5-fraction SBRT course, fiducial displacement was <7, 5, and 2 mm in 98%, 96%, and 67% of pretreatment CBCTs. CONCLUSIONS: ENB placement of embolization coils as fiducials for lung SBRT image guidance is associated with a low rate of iatrogenic pneumothoraces, and resulted in reliable placement of the fiducials in close proximity to the lung nodule. Embolization coils retained their relative position to the nodule throughout the course of SBRT, and provide an excellent alternative to linear gold seeds.

Neeves, K. B., Mccarty, O. J. T., Reininger, A. J., Sugimoto, M., & King, M. R. (2014). Flow-dependent thrombin and fibrin generation in vitro: Opportunities for standardization: Communication from SSC of the ISTH. *Journal of Thrombosis and Haemostasis, 12*(3), 418-420.

Netzer, G., & Sullivan, D. R. (2014). Recognizing, naming, and measuring a family intensive care unit syndrome. *Annals of the American Thoracic Society, 11*(3), 435-441.

Most major decisions in the intensive care unit (ICU) regarding goals of care are shared by clinicians and someone other than the patient. Multicenter clinical trials focusing on improved communication between clinicians and these surrogate decision makers have not reported consistently improved outcomes. We suggest that acquired maladaptive reasoning may contribute importantly to failure of the intervention strategies tested to date. Surrogate decision makers often suffer signi ficant psychological morbidity in the form of stress, anxiety, depression, and post-traumatic stress disorder. Family members in the ICU also suffer cognitive blunting and sleep deprivation. Their decision-making abilities are eroded by anticipatory grief and cognitive biases, while personal and family con flicts further impact their decision making. We propose recognizing a family ICU syndrome to describe the morbidity and associated decision-making impairment experienced bymany familymembers of patients with acute critical illness (in the ICU) and chronic critical illness (in the long-term, acute care hospital). Research rigorously using models of compromised decision making may help elucidate both mechanisms of impairment and targets for intervention. Better quantifying compromised decision making and its relationship to poor outcomes will allow us to formulate and advance useful techniques. The use of decision aids and improving ICU design may provide benefit now and in the near future. In measuring interventions targeting cognitive barriers, clinically significant outcomes, such as time to decision, should be considered. Statistical approaches, such as survival models and rank statistic testing, will increase our power to detect differences in our interventions.

Nguyen-Truong, C. K., Leo, M. C., Lee-Lin, F., Gedaly-Duff, V., Nail, L. M., Gregg, J., et al. (2014). Adaptation and testing of instruments to measure cervical cancer screening factors among vietnamese immigrant women. *Journal of Transcultural Nursing : Official Journal of the Transcultural Nursing Society / Transcultural Nursing Society*,

PURPOSE: Vietnamese American women diagnosed with cervical cancer are more likely to have advanced cancer than non-Hispanic White women. We sought to (a) develop a culturally sensitive Vietnamese translation of the Revised Susceptibility, Benefits, and Barriers Scale; Cultural Barriers to Screening Inventory; Confidentiality Issues Scale; and Quality of Care from the Health Care System Scale and (b) examine the psychometric properties. DESIGN: Cross-sectional study with 201 Vietnamese immigrant women from the Portland, Oregon, metropolitan area. METHOD: We used a community-based participatory research approach and the U.S. Census Bureau's team approach to translation. RESULTS: Cronbach's alpha ranged from .57 to .91. The incremental fit index ranged from .83 to .88. DISCUSSION AND CONCLUSIONS: The instruments demonstrated moderate to strong subscale internal consistency. Further research to assess structural validity is needed. IMPLICATIONS FOR PRACTICE: Our approaches to translation and psychometric examination support use of the instruments in Vietnamese immigrant women.

Nigg, J. T., & Craver, L. (2014). Commentary: ADHD and social disadvantage: An inconvenient truth? - a reflection on russell et al. () and larsson et al. (). *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 55*(5), 446-447.

In the 1950's, many experts believed hyperkinesis was a neurotic reaction to inner conflicts arising from early family experiences. In the 1990's, many experts believed ADHD to be 'genetic' (without a mechanistic explanation of what that meant). Both views appear naive today in a scientific world grappling with the complexity of highly plastic gene expression, gene x environment interplay, and epigenetic, context-dependent emergence of psychopathology. Both views also fail to account for the uncomfortable fact that ADHD is also associated with social disadvantage - a level of analysis required in a developmental psychopathology approach. That developmental psychopathology approach, pioneered a generation ago, initially emphasized the accumulation of risk and protective factors, and emerged in a contemporary systemic approach that seeks to determine whether it is risk accumulation (e.g., allostatic load) or specific risk factors (e.g., family process) that mechanistically shape psychopathology. Despite the prominence of the developmental psychopathology perspective, the social context of ADHD is surprisingly neglected today. Both Russell et al. (this issue, 2014) and Larsson et al. (this issue, 2014) take strides toward remedying this state of affairs.

Nygaard, E. B., Møller, C. L., Kievit, P., Grove, K. L., & Andersen, B. (2014). Increased fibroblast growth factor 21 expression in high-fat diet-sensitive non-human primates (macaca mulatta). *International Journal of Obesity*, *38*(2), 183-191.

Objective:Fibroblast growth factor 21 (FGF21) is a metabolic regulator of glucose and lipid metabolism. The physiological role of FGF21 is not yet fully elucidated, however, administration of FGF21 lowers blood glucose in diabetic animals. Moreover, increased levels of FGF21 are found in obese and diabetic rodents and humans compared with lean/non-diabetic controls.Methods:Adult male rhesus macaque monkeys were chronically maintained on a high-fat diet (HFD) or a standard diet (control, CTR). Plasma levels of FGF21, triglycerides and cholesterol were measured and body weight was record. Glucose-stimulated insulin secretion (GSIS) and glucose clearance was determined during an intravenous glucose tolerance test. Furthermore, expression of FGF21 and its receptors were determined in liver, pancreas, three white adipose tissues (WATs) and two skeletal muscles.Results:A cohort of the high-fat fed monkeys responded to the HFD with increasing body weight, plasma lipids, total cholesterol, GSIS and decreased glucose tolerance. These monkeys were termed HFD sensitive. Another cohort of monkeys did not become obese and maintained normal insulin sensitivity. These animals were defined as HFD resistant. Plasma FGF21 levels were significantly increased in all HFD fed monkeys compared with the CTR group. The HFD-sensitive monkeys showed a significant increase in FGF21 mRNA expression in all examined tissues compared with CTR, whereas FGF21 expression in the HFD-resistant group was only increased in the liver, pancreas and the retroperitoneal WAT. In the WAT, the co-receptor β-klotho was downregulated in the HFD-sensitive monkeys compared with the HFD-resistant group.Conclusion:This study demonstrates that HFD changes FGF21 and FGF21 receptor expression in a tissue-specific manner in rhesus monkeys; differential regulation is moreover observed between HFD-sensitive and -resistant monkeys. Monkeys that maintain normal levels of the FGF21 co-receptor β-klotho in the WAT on HFD were protected toward development of dyslipidemia and hyperglycemia. © 2014 Macmillan Publishers Limited.

Onega, T., Weaver, D., Geller, B., Oster, N., Tosteson, A. N. A., Carney, P. A., et al. (2014). Digitized whole slides for breast pathology interpretation: Current practices and perceptions. *Journal of Digital Imaging*,

Digital whole slide imaging (WSI) is an emerging technology for pathology interpretation; however, little is known about pathologists' practice patterns or perceptions regarding WSI. A national sample (N = 252) of pathologists from New Hampshire, Vermont, Washington, Oregon, Arizona, Alaska, Maine, and Minnesota were surveyed in this cross-sectional study (2011-2013). The survey included questions on pathologists' experience, WSI practice patterns, and perceptions using a six-point Likert scale. Agreement was summarized with descriptive statistics to characterize pathologists' use and perceptions of WSI. The majority of participating pathologists were males (63 %) between 40 and 59 years of age (70 %) and not affiliated with an academic medical center (72 %). Experience with WSI was reported by 49 %. Types of use reported included CME/board exams/teaching (28 %), tumor board/clinical conference (22 %), archival purposes (6 %), consultative diagnosis (4 %), research (4 %), and other uses (12 %). Most respondents (79 %) agreed that accurate diagnoses can be made with this technology, and that WSI is useful for obtaining a second opinion (88 %). However, 78 % of pathologists agreed that digital slides are too slow for routine clinical interpretation. Fifty-nine percent agreed that the benefits of WSI outweigh concerns. The respondents were equally split as to whether they would like to adopt WSI (51 %) or not (49 %). About half of pathologists reported experience with the WSI technology, largely for CME, licensure/board exams, and teaching. Positive perceptions regarding WSI slightly outweigh negative perceptions. Understanding practice patterns with WSI as dissemination advances may facilitate concordance of perceptions with adoption of the technology. 

O'Neil, M., Berkman, N., Hartling, L., Chang, S., Anderson, J., Motu'apuaka, M., et al. (2014). Observational evidence and strength of evidence domains: Case examples. *Systematic Reviews*, *3*(1), 35-4053-3-35.

BACKGROUND: Systematic reviews of healthcare interventions most often focus on randomized controlled trials (RCTs). However, certain circumstances warrant consideration of observational evidence, and such studies are increasingly being included as evidence in systematic reviews. METHODS: To illustrate the use of observational evidence, we present case examples of systematic reviews in which observational evidence was considered as well as case examples of individual observational studies, and how they demonstrate various strength of evidence domains

in accordance with current Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) methods guidance. RESULTS: In the presented examples, observational evidence is used when RCTs are infeasible or raise ethical concerns, lack generalizability, or provide insufficient data. Individual study case examples highlight how observational evidence may fulfill required strength of evidence domains, such as study limitations (reduced risk of selection, detection, performance, and attrition); directness; consistency; precision; and reporting bias (publication, selective outcome reporting, and selective analysis reporting), as well as additional domains of dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect). CONCLUSIONS: The cases highlighted in this paper demonstrate how observational studies may provide moderate to (rarely) high strength evidence in systematic reviews.

Oresanya, L., Makam, A. N., Belkin, M., Moneta, G. L., & Conte, M. S. (2014). Factors associated with primary vein graft occlusion in a multicenter trial with mandated ultrasound surveillance. *Journal of Vascular Surgery*, *59*(4), 996-1002.

Objective Even in the setting of duplex ultrasound (DUS) surveillance, a significant number of lower extremity vein bypass grafts (LEVBGs) become occluded as a first event. We sought to identify factors that may contribute to these primary occlusions. Methods This was a retrospective analysis of the Project of Ex Vivo Graft Engineering via Transfection III (PREVENT III) multicenter randomized clinical trial, in which 1404 patients with critical limb ischemia (CLI) underwent LEVBG with 1-year follow-up. Subjects were to undergo DUS at regular intervals (1, 3, 6, and 12 months), with reintervention based on prespecified DUS criteria. Patients who had nontechnical graft occlusion as the initial graft-related event were identified, and multivariate analysis was used to determine factors associated with primary graft occlusion. Results Primary vein graft occlusion occurred in 200 subjects and accounted for 36% of all primary patency events and 64% of all graft occlusions in the trial. Primary occlusion events were evenly distributed throughout the first postoperative year. Rates of recurrent CLI, loss of secondary patency, and major amputation in those with primary occlusion were 55%, 79%, and 22% respectively as compared to 18%, 10%, and 10% for subjects without primary occlusion (P <.001). On multivariate analysis, African-American race (subdistribution hazard ratio [SHR],

1.50; 95% confidence interval [CI], 1.06-2.12), a graft diameter <3 mm (SHR, 2.31; 95% CI, 1.33-4.01), and nonadherence with ultrasound surveillance (SHR, 1.58; 95% CI, 1.10-2.27) were independently associated with primary graft occlusion. Of the 123 subjects who received their last scheduled surveillance DUS prior to a primary occlusion event, 39 had a critical ultrasound abnormality identified but failed to undergo graft revision, while 84 had no critical ultrasound abnormality identified. Among these 84 subjects, female gender (SHR, 1.65; 95% CI, 1.07-2.54), and graft diameter <3 mm (SHR, 2.12; 95% CI, 1.03-4.37) were independent factors associated with unheralded graft occlusion. Conclusions Among patients undergoing LEVBG for CLI, almost half of primary patency events are occlusions even in the setting of a DUS surveillance protocol. African Americans, patients with smaller-diameter grafts, and those who are nonadherent with surveillance ultrasound are at increased risk. Failure to intervene on critical findings, and lack of sensitivity of DUS threshold criteria to predict thrombosis, are also important contributors. These findings suggest that prevention of vein graft thrombosis requires further improvements in risk stratification, surveillance, and the timing of reinterventions. 

Oyama, G., Okun, M. S., Schmidt, P., Tröster, A. I., Nutt, J., Go, C. L., et al. (2014). Deep brain stimulation may improve quality of life in people with parkinson's disease without affecting caregiver burden. *Neuromodulation, 17*(2), 126-131.

Objective This study aims to investigate the influence of deep brain stimulation (DBS) on caregiver burden and quality of life in Parkinson's disease. Methods A cross-sectional retrospective study utilizing the National Parkinson Foundation Quality Improvement Initiative clinical study was conducted. A group of 275 patients who had undergone DBS for Parkinson's disease were extracted from 2916 subjects who were included in this data base. The data were compared to an age, sex, and disease severity matched control group. A secondary analysis was then performed on two more control groups that were matched to account for presence or absence of motor fluctuations. The multidimensional caregiver strain index and Parkinson's disease quality-of-life questionnaire 39 summary index were compared. Results The multidimensional caregiver strain index did not differ between the DBS group (16.9 ± 11.8) and a matched non-DBS group (16.1 ± 17.6, p = 0.618). The quality-of-life index was, however,

significantly better in the DBS group (28.9 ± 15.6) than in the non-DBS group (32.3 ± 17.6, p = 0.034). A secondary analysis revealed that the total caregiver strain score was lower in the no motor fluctuation control group than the other two groups (p < 0.05). Regression analysis revealed significant relationships between the quality-of-life index and caregiver strain index total scores (p < 0.001), between caregiver strain index total score and age at surgery (p = 0.027), and also between the interval since surgery (p = 0.048). Conclusions Although there were several limitations to this study, DBS seems to improve quality of life without significantly increasing caregiver burden. © 2013 International Neuromodulation Society.

Parkinson Study Group SURE-PD Investigators, Schwarzschild, M. A., Ascherio, A., Beal, M. F., Cudkowicz, M. E., Curhan, G. C., et al. (2014). Inosine to increase serum and cerebrospinal fluid urate in parkinson disease: A randomized clinical trial. *JAMA Neurology, 71*(2), 141-150. IMPORTANCE: Convergent biological, epidemiological, and clinical data identified urate elevation as a candidate strategy for slowing disability progression in Parkinson disease (PD). OBJECTIVE: To determine the safety, tolerability, and urate-elevating capability of the urate precursor inosine in early PD and to assess its suitability and potential design features for a disease-modification trial. DESIGN, SETTING, AND PARTICIPANTS: The Safety of Urate Elevation in PD (SURE-PD) study, a randomized, double-blind, placebo-controlled, dose-ranging trial of inosine, enrolled participants from 2009 to 2011 and followed them for up to 25 months at outpatient visits to 17 credentialed clinical study sites of the Parkinson Study Group across the United States. Seventy-five consenting adults (mean age, 62 years; 55% women) with early PD not yet requiring symptomatic treatment and a serum urate concentration less than 6 mg/dL (the approximate population median) were enrolled. INTERVENTIONS: Participants were randomized to 1 of 3 treatment arms: placebo or inosine titrated to produce mild (6.1-7.0 mg/dL) or moderate (7.1-8.0 mg/dL) serum urate elevation using 500-mg capsules taken orally up to 2 capsules 3 times per day. They were followed for up to 24 months (median, 18 months) while receiving the study drug plus 1 washout month. MAIN OUTCOMES AND MEASURES: The prespecified primary outcomes were absence of unacceptable serious adverse events (safety), continued treatment without adverse event requiring dose reduction (tolerability), and elevation of urate assessed serially in serum and once (at 3 months) in cerebrospinal fluid. RESULTS Serious adverse events

(17), including infrequent cardiovascular events, occurred at the same or lower rates in the inosine groups relative to placebo. No participant developed gout and 3 receiving inosine developed symptomatic urolithiasis. Treatment was tolerated by 95% of participants at 6 months, and no participant withdrew because of an adverse event. Serum urate rose by 2.3 and 3.0 mg/dL in the 2 inosine groups (P < .001 for each) vs placebo, and cerebrospinal fluid urate level was greater in both inosine groups (P = .006 and <.001, respectively). Secondary analyses demonstrated nonfutility of inosine treatment for slowing disability. CONCLUSIONS AND RELEVANCE: Inosine was generally safe, tolerable, and effective in raising serum and cerebrospinal fluid urate levels in early PD. The findings support advancing to more definitive development of inosine as a potential disease-modifying therapy for PD. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00833690.

Peterson, A. L. (2014). A review of vitamin D and parkinson's disease. *Maturitas, 78*(1), 40-44.

The role of vitamin D in bone health has been known for over a century. More recent research has suggested that vitamin D may play a role in the muscular, immune, endocrine, and central nervous systems. Animal research suggests that vitamin D may have some protective effects against toxic insults that are known to damage dopamine cells, the primary cells to degenerate in PD. Persons with PD tend to have lower vitamin D levels than persons of similar ages without PD. Vitamin D levels are generally associated with bone mineral density (BMD) in persons with PD, but simply giving vitamin D does not appear to improve BMD. Results of genetic studies examining polymorphism of the vitamin D receptor and PD risk, severity, or age at onset have shown variable results, with FokI CC seeming to possibly carry some increased risk of PD. Amount of sun exposure and vitamin D levels in earlier life may influence the risk of developing PD. Cross-sectional research suggests a relationship between vitamin D levels and severity of PD symptoms. A single intervention study did show some improvement in PD with vitamin D supplementation. Vitamin D may have effects on PD symptoms and perhaps even on the risk of disease development or disease progression. More well designed intervention studies are needed to confirm the effect of vitamin D on PD symptoms. Human neuroprotection studies are needed, but probably not feasible until better biomarkers are established.

Pettit, K. E., Tran, S. H., Lee, E., & Caughey, A. B. (2014). The association of antenatal corticosteroids with neonatal hypoglycemia and hyperbilirubinemia. *Journal of Maternal-Fetal and Neonatal Medicine, 27*(7), 683-686.

Objective: While antenatal corticosteroids reduce the risk of neonatal morbidity and mortality, perhaps the maternal hyperglycemia they produce has other neonatal effects. Thus, we sought to examine the association between antenatal betamethasone exposure and neonatal hypoglycemia and hyperbilirubinemia. Methods: We designed a retrospective cohort study of all preterm deliveries from 32 to 37 weeks of gestation at a single university hospital from 1990 to 2007. Data were collected on antenatal betamethasone administration and the neonatal outcomes. Univariable, multivariable and stratified analyses were conducted. Results: Of 6675 preterm deliveries, significantly higher rates of neonatal hypoglycemia (5.7% versus 4.2%, $p<0.05$) and hyperbilirubinemia (45.9% versus 24.1%, $p<0.05$) were observed in neonates exposed to antenatal betamethasone. Controlling for potential confounders including gestational age, these findings persisted with betamethasone-exposed neonates 1.6 times more likely to have hypoglycemia (aOR 1.60, 95% CI 1.24-2.07) and 3.2 times more likely to have hyperbilirubinemia (aOR 3.23, 95% CI 2.92-3.58). Conclusions: Antenatal betamethasone was associated with neonatal hypoglycemia and hyperbilirubinemia. Further work to determine whether this association is related to maternal hyperglycemia should be conducted, given this could be addressed with strict maternal glycemic control during betamethasone administration. © 2014 Informa UK Ltd. All rights reserved: reproduction in whole or part not permitted.

Phillips, K. G., Baker-Groberg, S. M., & McCarty, O. J. (2014). Quantitative optical microscopy: Measurement of cellular biophysical features with a standard optical microscope. *Journal of Visualized Experiments : JoVE, (86). doi*(86), 10.3791/50988.

We describe the use of a standard optical microscope to perform quantitative measurements of mass, volume, and density on cellular specimens through a combination of bright field and differential interference contrast imagery. Two primary approaches are presented: noninterferometric quantitative phase microscopy (NIQPM), to perform measurements of total cell mass and subcellular density distribution, and Hilbert transform differential interference contrast microscopy (HTDIC) to determine volume. NIQPM is based on a simplified model of wave

propagation, termed the paraxial approximation, with three underlying assumptions: low numerical aperture (NA) illumination, weak scattering, and weak absorption of light by the specimen. Fortunately, unstained cellular specimens satisfy these assumptions and low NA illumination is easily achieved on commercial microscopes. HTDIC is used to obtain volumetric information from through-focus DIC imagery under high NA illumination conditions. High NA illumination enables enhanced sectioning of the specimen along the optical axis. Hilbert transform processing on the DIC image stacks greatly enhances edge detection algorithms for localization of the specimen borders in three dimensions by separating the gray values of the specimen intensity from those of the background. The primary advantages of NIQPM and HTDIC lay in their technological accessibility using "off-the-shelf" microscopes. There are two basic limitations of these methods: slow z-stack acquisition time on commercial scopes currently abrogates the investigation of phenomena faster than 1 frame/minute, and secondly, diffraction effects restrict the utility of NIQPM and HTDIC to objects from 0.2 up to 10 (NIQPM) and 20 (HTDIC) mum in diameter, respectively. Hence, the specimen and its associated time dynamics of interest must meet certain size and temporal constraints to enable the use of these methods. Excitingly, most fixed cellular specimens are readily investigated with these methods.

Picard, N., Trompf, K., Yang, C. -., Miller, R. L., Carrel, M., Loffing-Cueni, D., et al. (2014). Protein phosphatase 1 inhibitor-1 deficiency reduces phosphorylation of renal NaCl cotransporter and causes arterial hypotension. *Journal of the American Society of Nephrology*, *25*(3), 511-522.
The thiazide-sensitive NaCl cotransporter (NCC) of the renal distal convoluted tubule (DCT) controls ion homeostasis and arterial BP. Loss-of-function mutations of NCC cause renal salt wasting with arterial hypotension (Gitelman syndrome). Conversely, mutations in the NCC-regulating WNK kinases or kelch-like 3 protein cause familial hyperkalemic hypertension. Here, we performed automated sorting of mouse DCTs and microarray analysis for comprehensive identification of novel DCT-enriched gene products, which may potentially regulate DCT and NCC function. This approach identified protein phosphatase 1 inhibitor-1 (I-1) as a DCT-enriched transcript, and immunohistochemistry revealed I-1 expression in mouse and human DCTs and thick ascending limbs. In heterologous expression systems, coexpression of NCC with I-1 increased thiazide-dependent Na+ uptake, whereas RNAi-mediated knockdown of endogenous I-

1 reduced NCC phosphorylation. Likewise, levels of phosphorylated NCC decreased by approximately 50% in I-1 (I-1-/-) knockout mice without changes in total NCC expression. The abundance and phosphorylation of other renal sodium-transporting proteins, including NaPi-IIa, NKCC2, and ENaC, did not change, although the abundance of pendrin increased in these mice. The abundance, phosphorylation, and subcellular localization of SPAK were similar in wild-type (WT) and I-1-/- mice. Compared with WT mice, I-1-/- mice exhibited significantly lower arterial BP but did not display other metabolic features of NCC dysregulation. Thus, I-1 is a DCT-enriched gene product that controls arterial BP, possibly through regulation of NCC activity. 

Piedra, M. P., Nemecek, A. N., & Ragel, B. T. (2014). Timing of cranioplasty after decompressive craniectomy for trauma. *Surgical Neurology International, 5*(FEB)

Background: The optimal timing of cranioplasty after decompressive craniectomy for trauma is unknown. The aim of this study was to determine if early cranioplasty after decompressive craniectomy for trauma reduces complications. Methods: Consecutive cases of patients who underwent autologous cranioplasty after decompressive craniectomy for trauma at a single Level I Trauma Center were studied in a retrospective 10 year data review. Associations of categorical variables were compared using Chi-square test or Fisher's exact test. Results: A total of 157 patients were divided into early (<12 weeks; 78 patients) and late (≥12 weeks; 79 patients) cranioplasty cohorts. Baseline characteristics were similar between the two cohorts. Cranioplasty operative time was significantly shorter in the early (102 minutes) than the late (125 minutes) cranioplasty cohort (P = 0.0482). Overall complication rate in both cohorts was 35%. Infection rates were lower in the early (7.7%) than the late (14%) cranioplasty cohort as was bone graft resorption (15% early, 19% late), hydrocephalus rate (7.7% early, 1.3% late), and postoperative hematoma incidence (3.9% early, 1.3% late). However, these differences were not statistically significant. Patients <18 years of age were at higher risk of bone graft resorption than patients ≥18 years of age (OR 3.32, 95% CI 1.25-8.81; P = 0.0162). Conclusions: After decompressive craniectomy for trauma, early (<12 weeks) cranioplasty does not alter the incidence of complication rates. In patients <18 years of age, early (<12 weeks) cranioplasty increases the

risk of bone resorption. Delaying cranioplasty (≥12 weeks) results in longer operative times and may increase costs. Copyright: © 2014 Roohi F.

Piper, B. J., Gray, H. M., Raber, J., & Birkett, M. A. (2014). Reliability and validity the brief problem monitor, an abbreviated form of the child behavior checklist. *Psychiatry and Clinical Neurosciences*,

AIM: The parent form of the 113 item Child Behavior Checklist (CBCL) is widely utilized by child psychiatrists and psychologists. This report examines the reliability and validity of a recently developed abbreviated version of the CBCL, the Brief Problem Monitor (BPM). METHODS: Caregivers (N=567) completed the CBCL online and the 19 BPM items were examined separately. RESULTS: Internal consistency of the BPM was high (Cronbach's alpha=0.91) and satisfactory for the Internalizing (0.78), Externalizing (0.86), and Attention (0.87) scales. High correlations between the CBCL and BPM were identified for the total score (r=0.95) as well as the Internalizing (0.86), Externalizing (0.93), and Attention (0.97) scales. The BPM and scales were sensitive and identified significantly higher behavioral and emotional problems among children whose caregiver reported a psychiatric diagnosis of Attention Deficit Hyperactivity Disorder, bipolar, depression, anxiety, developmental disabilities, or Autism Spectrum Disorders relative to a comparison group that had not been diagnosed with these disorders. BPM ratings also differed by the socioeconomic status and education of the caregiver. Mothers with higher annual incomes rated their children as having 38.8% fewer total problems (Cohen's d=0.62) as well as 42.8% lower Internalizing (d=0.53), 44.1% less Externalizing (d=0.62), and 30.9% decreased Attention (d=0.39). A similar pattern was evident for maternal education (d=0.30 to 0.65). CONCLUSION: Overall, these findings provide strong psychometric support for the BPM although the differences based on the characteristics of the parent indicates that additional information from other sources (e.g., teachers) should be obtained to complement parental reports.

Price, D., Bateman, E. D., Chisholm, A., Papadopoulos, N. G., Bosnic-Anticevich, S., Pizzichini, E., et al. (2014). Complementing the randomized controlled trial evidence base: Evolution not revolution. *Annals of the American Thoracic Society*, *11*(SUPPL. 2), S92-S98.

Observational studies and pragmatic trials can complement classical randomized controlled trials

(RCTs) by providing data more relevant to the circumstances under which medicine is routinely practiced, thereby providing practical guidance for clinicians. The bearing of RCT findings on day-to-day practice can be weighted and the data more meaningfully interpreted by practicing clinicians if evidence is integrated from a variety of different study designs and methodologies. The advent of observational studies and pragmatic trials, often referred to as "real-life studies," has met with a degree of cynicism, but their role and value is gaining widespread recognition and support among clinicians. This article discusses where observational studies and pragmatic trials have utility, namely: in addressing clinical questions that are unanswered and/or unanswerable by RCTs; in testing new hypotheses and possible license extensions; and in helping to differentiate between available therapies for a given indication. Moreover, it seeks to highlight how the different approaches fit within a conceptual framework of evidence relevant to clinical practice, a step-change in the traditional view of medical evidence. 

Probst, M. A., Mower, W. R., Kanzaria, H. K., Hoffman, J. R., Buch, E. F., & Sun, B. C. (2014). Analysis of emergency department visits for palpitations (from the national hospital ambulatory medical care survey). *The American Journal of Cardiology*,

Palpitations is a common complaint in patients who visit the emergency department (ED), with causes ranging from benign to life threatening. We analyzed the ED component of the National Hospital Ambulatory Medical Care Survey for 2001 through 2010 for visits with a chief complaint of palpitations and calculated nationally representative weighted estimates for prevalence, demographic characteristics, and admission rates. ED and hospital discharge diagnoses were tabulated and categorized, and recursive partitioning was used to identify factors associated with admission. An estimated 684,000 visits had a primary reason for visit of "palpitations" representing a national prevalence of 5.8 per 1,000 ED visits (0.58%, 95% confidence interval 0.52 to 0.64). Women and non-Hispanic whites were responsible for most visits. A cardiac diagnosis made up 34% of all ED diagnoses. The overall admission rate was 24.6% (95% confidence interval 21.2 to 28.1), with higher rates seen in the Midwest and Northeast compared with the West. Survey-weighted recursive partitioning revealed several factors associated with admission including age >50 years, male gender, cardiac ED diagnosis, tachycardia,

hypertension, and Medicare insurance. In conclusion, palpitations are responsible for a significant minority of ED visits and are associated with a cardiac diagnosis roughly 1/3 of the time. This was associated with a relatively high admission rate, although significant regional variation in these rates exists.

Pugh, M. J., Orman, J. A., Jaramillo, C. A., Salinsky, M. C., Eapen, B. C., Towne, A. R., et al. (2014). The prevalence of epilepsy and association with traumatic brain injury in veterans of the afghanistan and iraq wars. *The Journal of Head Trauma Rehabilitation*,
OBJECTIVE:: To examine the association of epilepsy with traumatic brain injury (TBI) in Afghanistan and Iraq (Operation Enduring Freedom [OEF]/Operation Iraqi Freedom [OIF]) Veterans. DESIGN:: Cross-sectional observational study. PARTICIPANTS:: A total 256284 OEF/OIF Veterans who received inpatient and outpatient care in the Veterans Health Administration in fiscal years 2009-2010. MAIN OUTCOME MEASURES:: We used algorithms developed for use with International Classification of Diseases, Ninth Revision, Clinical Modification, codes to identify epilepsy, TBI (penetrating TBI [pTBI]/other TBI), and other risk factors for epilepsy (eg, stroke). TBI and other risk factors were identified prior to the index date (first date of seizure or October 1, 2009) for primary analyses. RESULTS:: Epilepsy prevalence was 10.6 per 1000 (N = 2719) in fiscal year 2010; age-adjusted prevalence was 6.1. Of 37718 individuals with a diagnosis of TBI, 29297 Veterans had a diagnosis of TBI prior to the index date. Statistically significant associations were found between epilepsy and prior TBI diagnosis (pTBI: adjusted odds ratio = 18.77 [95% confidence interval, 9.21-38.23]; other TBI: adjusted odds ratio = 1.64 [1.43-1.89]). CONCLUSIONS:: Among OEF/OIF Veterans, epilepsy was associated with previous TBI diagnosis, with pTBI having the strongest association. Because war-related epilepsy in Vietnam War Veterans with TBI continued 35 years postwar, a detailed, prospective study is needed to understand the relationship between epilepsy and TBI severity in OEF/OIF Veterans.

Purnell, J. Q., Lahna, D. L., Samuels, M. H., Rooney, W. D., & Hoffman, W. F. (2014). Loss of pons-to-hypothalamic white matter tracks in brainstem obesity. *International Journal of Obesity (2005)*,
Hyperphagia and obesity have been reported following damage to the hypothalamus in humans.

Other brain sites are also postulated to be involved in the control of food intake and body weight regulation, such as the amygdala and brainstem. The brainstem, however, is thought to primarily integrate short-term meal-related signals but not affect long-term alterations in body weight, which is controlled by higher centers. The objective of this study was to identify structural pathways damaged in a patient with a brainstem cavernoma who experienced sudden onset of hyperphagia and greater than 50 kg weight gain in less than one year following surgical drainage via a midline suboccipital craniotomy. Diffusion tensor imaging revealed loss of nerve fiber connections between her brainstem, hypothalamus, and higher brain centers with preservation of motor tracks. Imaging and endocrine testing confirmed normal hypothalamic structure and function. Gastric bypass surgery restored normal appetite and body weight to baseline. This is the first report of 'brainstem obesity' and adds to the brain regions that can determine the long-term body weight set point in humans.International Journal of Obesity accepted article peview online, 14 April 2014. doi:10.1038/ijo.2014.57.

Qaseem, A., Chou, R., Humphrey, L. L., & Shekelle, P. (2014). Inpatient glycemic control: Best practice advice from the clinical guidelines committee of the american college of physicians. *American Journal of Medical Quality, 29*(2), 95-98.

Hyperglycemia is associated with poor outcomes in hospitalized medical and surgical patients. Although some early evidence showed benefits of intensive insulin therapy (IIT), recent evidence does not show a consistent benefit and even shows harm associated with the use of IIT. The overuse of some therapeutic interventions and the resulting harms to a patient are an important component of unnecessary health care costs. The goal of this article is to address the management of hyperglycemia and evaluate the benefits and harms associated with the use of IIT to achieve tight glycemic control in hospitalized patients with or without diabetes mellitus. This article is based on the evidence review and the guideline developed by the American College of Physicians on this topic. Best Practice Advice 1: Clinicians should target a blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in SICU/MICU patients. Best Practice Advice 2: Clinicians should avoid targets less than 7.8 mmol/L (<140mg/dL) because harms are likely to increase with lower blood glucose targets. © 2013 by the American College of Medical Quality.

Qiu, J., Zhang, C., Borgquist, A., Nestor, C. C., Smith, A. W., Bosch, M. A., et al. (2014). Insulin excites anorexigenic proopiomelanocortin neurons via activation of canonical transient receptor potential channels. *Cell Metabolism, 19*(4), 682-693.

Proopiomelanocortin (POMC) neurons within the hypothalamic arcuate nucleus are vital anorexigenic neurons. Although both the leptin and insulin receptors are coupled to the activation of phosphatidylinositide 3 kinase (PI3K) in POMC neurons, they are thought to have disparate actions on POMC excitability. Using whole-cell recording and selective pharmacological tools, we have found that, similar to leptin, purified insulin depolarized POMC and adjacent kisspeptin neurons via activation of TRPC5 channels, which are highly expressed in these neurons. In contrast, insulin hyperpolarized and inhibited NPY/AgRP neurons via activation of KATP channels. Moreover, Zn(2+), which is found in insulin formulations at nanomolar concentrations, inhibited POMC neurons via activation of KATP channels. Finally, as predicted, insulin given intracerebroventrically robustly inhibited food intake and activated c-fos expression in arcuate POMC neurons. Our results show that purified insulin excites POMC neurons in the arcuate nucleus, which we propose is a major mechanism by which insulin regulates energy homeostasis.

Raber, J., Rudobeck, E., Campbell-Beachler, M., Allen, A. R., Allen, B., Rosi, S., et al. (2014). Silicon radiation-induced enhancement of synaptic plasticity in the hippocampus of naive 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 naive 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 naive mice) and animals exposed to the contextual freezing test (cognitively tested mice). In behaviorally naive 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.

Rackham, D. M., C. Herink, M., Stevens, I. G., Cardoza, N. M., & Singh, H. (2014). Evidence behind FDA alerts for drugs with adverse cardiovascular effects: Implications for clinical practice. *Pharmacotherapy*, *34*(4), 358-372.

The U.S. Food and Drug Administration (FDA) periodically publishes Drug Safety Communications and Drug Alerts notifying health care practitioners and the general public of important information regarding drug therapies following FDA approval. These alerts can result in both positive and negative effects on patient care. Most clinical trials are not designed to detect long-term safety end points, and postmarketing surveillance along with patient reported events are often instrumental in signaling the potential harmful effect of a drug. Recently, many cardiovascular (CV) safety announcements have been released for FDA-approved drugs. Because a premature warning could discourage a much needed treatment or prompt a sudden discontinuation, it is essential to evaluate the evidence supporting these FDA alerts to provide effective patient care and to avoid unwarranted changes in therapy. Conversely, paying attention to these warnings in cases involving high-risk patients can prevent adverse effects and litigation. This article reviews the evidence behind recent FDA alerts for drugs with adverse CV effects and discusses the clinical practice implications. 

Ravindran, A., Mohammed, J., Gunderson, A. J., Cui, X., & Glick, A. B. (2014). Tumor-promoting role of TGFß1 signaling in ultraviolet B-induced skin carcinogenesis is associated with cutaneous inflammation and lymph node migration of dermal dendritic cells. *Carcinogenesis*, *35*(4), 959-

966.

Transforming growth factor beta 1 (TGFß1) is a pleiotropic cytokine in the skin that can function both as a tumor promoter and suppressor in chemically induced skin carcinogenesis, but the function in ultraviolet B (UVB) carcinogenesis is not well understood. Treatment of SKH1 hairless mice with the activin-like kinase 5 (ALK5) inhibitor SB431542 to block UVB-induced activation of cutaneous TGFß1 signaling suppressed skin tumor formation but did not alter tumor size or tumor cell proliferation. Tumors that arose in SB-treated mice after 30 weeks had significantly reduced percentage of IFNγ+ tumor-infiltrating lymphocytes compared with control mice. SB431542 blocked acute and chronic UVB-induced skin inflammation and T-cell activation in the skindraining lymph node (SDLN) and skin but did not alter UVBinduced epidermal proliferation. We tested the effect of SB431542 on migration of skin dendritic cell (DC) populations because DCs are critical mediators of T-cell activation and cutaneous inflammation. SB431542 blocked (i) UVB-induced Smad2 phosphorylation in dermal DC (dDC) and (ii) SDLN and ear explant migration of CD103+ CD207+ and CD207- skin DC subsets but did not affect basal or UV-induced migration of Langerhans cells. Mice expressing a dominant-negative TGFß type II receptor in CD11c+ cells had reduced basal and UVB-induced SDLN migration of CD103+ CD207+ and CD207- DC subsets and a reduced percentage of CD86high dDC following UVB irradiation. Together, these suggest that TGFß1 signaling has a tumor-promoting role in UVB-induced skin carcinogenesis and this is mediated in part through its role in UVB-induced migration of dDC and cutaneous inflammation.


Raybuck, J. D., & Lattal, K. M. (2014). Differential effects of dorsal hippocampal inactivation on expression of recent and remote drug and fear memory. *Neuroscience Letters, 569C*, 1-5.

Drugs of abuse generate strong drug-context associations, which can evoke powerful drug cravings that are linked to reinstatement in animal models and to relapse in humans. Work in learning and memory has demonstrated that contextual memories become more distributed over time, shifting from dependence on the hippocampus for retrieval to dependence on cortical structures. Implications for such changes in the structure of memory retrieval to addiction are unknown. Thus, to determine if the passage of time alters the substrates of conditioned place preference (CPP) memory retrieval, we investigated the effects of inactivation of the dorsal

hippocampus (DH) with the GABA-A receptor agonist muscimol on expression of recent or remote CPP. We compared these effects with the same manipulation on expression of contextual fear conditioning. DH inactivation produced similar deficits in expression of both recent and remote CPP, but blocked expression of recent but not remote contextual fear memory. We describe the implications of these findings for mechanisms underlying long-term storage of contextual information.

Reddy, P. H. (2014). Increased mitochondrial fission and neuronal dysfunction in huntington's disease: Implications for molecular inhibitors of excessive mitochondrial fission. *Drug Discovery Today*, Huntington's disease (HD) is a fatal, progressive neurodegenerative disease with an autosomal dominant inheritance, characterized by chorea, involuntary movements of the limbs and cognitive impairments. Since identification of the HD gene in 1993, tremendous progress has been made in identifying underlying mechanisms involved in HD pathogenesis and progression, and in developing and testing molecular therapeutic targets, using cell and animal models of HD. Recent studies have found that mutant Huntingtin (mHtt) interacts with Dynamin-related protein 1 (Drp1), causing excessive fragmentation of mitochondria, leading to abnormal mitochondrial dynamics and neuronal damage in HD-affected neurons. Some progress has been made in developing molecules that can reduce excessive mitochondrial fission while maintaining both the normal balance between mitochondrial fusion and fission, and normal mitochondrial function in diseases in which excessive mitochondrial fission has been implicated. In this article, we highlight investigations that are determining the involvement of excessive mitochondrial fission in HD pathogenesis, and that are developing inhibitors of excessive mitochondrial fission for potential therapeutic applications.

Reddy, P. H. (2014). Misfolded proteins, mitochondrial dysfunction, and neurodegenerative diseases. *Biochimica Et Biophysica Acta*,

Reddy, R. C., Estill, C. T., Meaker, M., Stormshak, F., & Roselli, C. E. (2014). Sex differences in expression of oestrogen receptor alpha but not androgen receptor mRNAs in the foetal lamb brain. *Journal of Neuroendocrinology*, *26*(5), 321-328.

Gonadal steroid hormones play important roles during critical periods of development to organise

brain structures that control sexually dimorphic neuroendocrine responses and behaviours. Specific receptors for androgens and oestrogens must be expressed at appropriate times during development to mediate these processes. The present study was performed to test for sex differences in the relative expression of oestrogen receptor (ER)alpha and androgen receptor (AR) mRNA during the window of time in gestation that is critical for behavioural masculinisation and differentiation of the ovine sexually dimorphic nucleus (oSDN) in the sheep. In addition, we examined whether ERalpha and AR mRNA expression is localised within the nascent oSDN and could be involved in its development. Using the quantitative real-time polymerase chain reaction, we found that females expressed more ERalpha mRNA than males in medial preoptic area and medial basal hypothalamus during the mid-gestational critical period for brain sexual differentiation. No sex differences were found for AR mRNA in any tissue examined or for ERalpha in amygdala and frontal cortex. Using radioactive in situ hybridisation, we found that the distributions of ERalpha and AR mRNA overlapped with aromatase mRNA, which delineates the boundaries of the developing oSDN and identifies this nucleus as a target for both androgens and oestrogens. These data demonstrate that the transcriptional machinery for synthesising gonadal steroid receptors is functional in the foetal lamb brain during the critical period for sexual differentiation and suggest that possible mechanisms for establishing dimorphisms controlled by gonadal steroids may exist at the level of steroid hormone receptor expression.

Reeves, M. F., Blumenthal, P. D., Jones, R. K., Nichols, M. D., & Saporta, V. A. (2014). New research at the 2014 national abortion federation annual meeting: Continuously improving abortion care. *Contraception*,

Rennie, M. Y., Gahan, C. G., Lopez, C. S., Thornburg, K. L., & Rugonyi, S. (2014). 3D imaging of the early embryonic chicken heart with focused ion beam scanning electron microscopy. *Microscopy and Microanalysis : The Official Journal of Microscopy Society of America, Microbeam Analysis Society, Microscopical Society of Canada*, , 1-9.

Early embryonic heart development is a period of dynamic growth and remodeling, with rapid changes occurring at the tissue, cell, and subcellular levels. A detailed understanding of the events that establish the components of the heart wall has been hampered by a lack of

methodologies for three-dimensional (3D), high-resolution imaging. Focused ion beam scanning electron microscopy (FIB-SEM) is a novel technology for imaging 3D tissue volumes at the subcellular level. FIB-SEM alternates between imaging the block face with a scanning electron beam and milling away thin sections of tissue with a FIB, allowing for collection and analysis of 3D data. FIB-SEM was used to image the three layers of the day 4 chicken embryo heart: myocardium, cardiac jelly, and endocardium. Individual images obtained with FIB-SEM were comparable in quality and resolution to those obtained with transmission electron microscopy. Up to 1,100 serial images were obtained in 4 nm increments at 4.88 nm resolution, and image stacks were aligned to create volumes 800-1,500 mum3 in size. Segmentation of organelles revealed their organization and distinct volume fractions between cardiac wall layers. We conclude that FIB-SEM is a powerful modality for 3D subcellular imaging of the embryonic heart wall.

Riddle, M. C., Aronson, R., Home, P., Marre, M., Niemoeller, E., Miossec, P., et al. (2013). Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: A 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes Care*, *36*(9), 2489-2496.

OBJECTIVE: To examine the efficacy and safety of adding the once-daily glucagon-like peptide-1 receptor agonist (GLP-1RA) lixisenatide to established basal insulin therapy alone or together with metformin, in people with type 2 diabetes and elevated glycated hemoglobin (HbA1c). RESEARCH DESIGN AND METHODS: We conducted a double-blind, parallel-group, placebo-controlled trial. Patients (n = 495) with established basal insulin therapy but inadequate glycemic control were randomized to add lixisenatide 20 mug or placebo for 24 weeks. Basal insulin dosage was unchanged except to limit hypoglycemia. HbA1c reduction from baseline was the primary end point. RESULTS: Mean duration of diabetes was 12.5 years, duration of insulin use was 3.1 years, insulin dosage was 55 units/day, and baseline HbA1c was 8.4%. With lixisenatide, the placebo-corrected change of HbA1c from baseline was -0.4% (95% CI -0.6 to -0.2; P = 0.0002), and mean HbA1c at end point was 7.8%. HbA1c <7.0% (53 mmol/mol) was attained by more lixisenatide (28%) than placebo (12%; P < 0.0001) participants. Lixisenatide reduced plasma glucose levels after a standardized breakfast (placebo-corrected reduction, -3.8 mmol/L;

P < 0.0001); seven-point glucose profiles showed a reduction persisting through the day. Reductions in body weight (placebo corrected, -1.3 kg; P < 0.0001) and insulin dosage (-3.7 units/day; P = 0.012) were greater with lixisenatide. Main adverse events (AEs) with lixisenatide were gastrointestinal. Symptomatic hypoglycemia was 28% for lixisenatide and 22% for placebo; 4 of 328 subjects (1.2%) had severe hypoglycemia with lixisenatide vs. 0 of 167 with placebo. CONCLUSIONS: By improving HbA1c and postprandial hyperglycemia without weight gain in type 2 diabetes with inadequate glycemic control despite stable basal insulin, lixisenatide may provide an alternative to rapid-acting insulin or other treatment options.

Riddle, M. C., Rosenstock, J., Vlajnic, A., & Gao, L. (2014). Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: Twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes, Obesity and Metabolism*, *16*(5), 396-402.

Aim: Many patients with type 2 diabetes mellitus (T2DM) initiate insulin therapy when other treatments fail; how best to do this is poorly defined. Methods: People with T2DM [n=588; glycated haemoglobin A1C (A1C) >7.0%, mean baseline 9.4%] were randomized to twice-daily premixed protamine-aspart/aspart insulin (PM-2), once-daily insulin glargine plus zero to one prandial insulin glulisine injection (G+1), or insulin glargine plus zero to three prandial injections (G+3). Insulin was titrated for 60weeks. Efficacy and safety outcomes were assessed. Results: Discontinuation rates were 53 of the 194 (27%), 44 of the 194 (23%) and 38 of the 194 (20%), for PM-2, G+1 and G+3. Glycaemic control improved in all groups (A1C 7.2±1.37, 7.1±1.68 and 7.0±1.21% at 60weeks; 7.5±1.29, 7.2±1.62 and 7.2±1.63% at endpoint). G+1 was statistically non-inferior to PM-2 in reducing A1C. G+3 was slightly superior to PM-2 in attaining <7.0% at 60weeks, but only when the analysis included Good Clinical Practice non-adherent sites. Hypoglycaemia with plasma glucose <2.8mmol/l was more frequent with PM-2 versus G+1 and G+3; [adjusted incidence: 46 (p=0.0087) vs. 33 (p=0.0045) and 31.5%; events per patient-year: 1.9 vs. 0.8 and 0.9, p≤0.0001]. Insulin dosage and weight-gain were similar. Conclusion: Basal insulin plus a single prandial injection is as effective in improving glycaemic control as premixed insulin. Full basal-prandial therapy is only slightly more effective than premixed insulin.

Stepwise basal-prandial regimens improve glycaemic control with less hypoglycaemia than twice-daily premixed insulin. © 2013 John Wiley & Sons Ltd.

Riley, A. R., & Gaynor, S. T. (2014). Identifying mechanisms of change: Utilizing single-participant methodology to better understand behavior therapy for child depression. *Behavior Modification*, This study examined therapeutic mechanisms of action at the single-participant level in a behavior therapy (BT) for youth depression. By controlling for non-specific early responses, identifying potential mechanisms of action a priori, taking frequent measures of hypothesized mechanisms and dependent variables, rigorously evaluating internal validity, and using a variety of analytic methods, a unique model for analysis of potential mediators was created. Eleven children (M age = 9.84) meeting criteria on the Children's Depression Rating Scale-Revised (M = 55.36) and Children's Depression Inventory (M = 23.45) received non-directive therapy (NDT), followed by BT for those still displaying significant symptoms. Four participants (36%) had a clinically significant response to NDT. For the remaining seven, statistically significant changes in depressive symptoms and family interactions during the BT interval were found at the group level. At the single-participant level, evidence suggesting that outcome was at least partially mediated by changes in treatment targets was obtained for four of seven (57%). As the field further embraces efforts to learn not only whether treatments work but also how they work, the single-participant approach to evaluating mediators provides a useful framework for evaluating theories of therapeutic change.

Rosenbaum, B. P., Kelly, M. L., Kshettry, V. R., Vadera, S., & Weil, R. J. (2014). Practice patterns of in-hospital surgical treatment of trigeminal neuralgia from 1988 to 2010. *Clinical Neurology and Neurosurgery*, *120*, 55-63.

OBJECTIVE: Neurosurgeons have a variety of procedures to offer when treating medically intractable trigeminal neuralgia (TN). We reviewed the national trends in procedural volume for in-hospital treatment of TN. METHODS: The Nationwide Inpatient Sample (1988-2010) provided data on patients hospitalized with a principal diagnosis of TN and a related principal procedure. We categorized principal procedures as open, other, percutaneous, or radiosurgery. RESULTS: We identified 13,466 relevant hospital admissions. The volume for open procedures and

radiosurgery remained relatively constant, whereas percutaneous procedures decreased. Mean age of patients undergoing percutaneous and radiosurgery procedures (67.9 and 69.5 years) was higher than open and other procedures (60.4 and 63.4 years) (p-value <0.001). The mean total in-hospital inflation-adjusted charges for all four categories increased over time (p-values <0.001). The mean total in-hospital inflation-adjusted charge for radiosurgery ($37,666) was higher than open ($28,046) procedures (p-value <0.001). CONCLUSIONS: Patients who undergo an open procedure to treat TN are younger than those who undergo a percutaneous or a radiosurgery procedure. The perceived risk of open surgery in older patients may drive offering percutaneous or radiosurgical procedures. In addition, the in-hospital inflation-adjusted charges for all procedures increased over time, with radiosurgery being higher than those of open procedures.

Rowland, M., Peterson-Besse, J., Dobbertin, K., Walsh, E. S., Horner-Johnson, W., & The Expert Panel on Disability and Health Disparities. (2014). Health outcome disparities among subgroups of people with disabilities: A scoping review. *Disability and Health Journal, 7*(2), 136-150. BACKGROUND: A growing body of research has found that people with disabilities experience lower health status and an excess burden of disease relative to the general US population. However, the population of people with disabilities is quite diverse. Thus, it is important to understand health differences between subgroups of people with disabilities in order to most effectively target interventions to address disparities. An initial step in this process is reviewing and synthesizing available research addressing these subgroup differences. OBJECTIVES: To conduct a scoping review of literature to describe recent research activity that has examined health outcome disparities within populations of people with disabilities. METHODS: We searched for relevant articles in MEDLINE, PsycINFO, and CINAHL databases. Three staff independently reviewed abstracts according to inclusion criteria. Two authors then independently extracted data from each included article. RESULTS: For many of the health outcomes of interest, there was no published literature in relation to key disparity factors (e.g. race, income) within the population of people with disabilities. The health outcomes most frequently examined were diabetes and heart disease. The most frequently examined disparity factors were the type of disabling condition and gender. CONCLUSIONS: There are significant gaps in available research. Building a body of

research that identifies disparities and potentially vulnerable subgroups may improve understanding of the causes of disparities and contribute to efforts to improve quality of life and health outcomes for individuals with disabilities.

Rynko, A. E., Fryer, A. D., & Jacoby, D. B. (2014). Interleukin-1beta mediates virus-induced M2 muscarinic receptor dysfunction and airway hyperreactivity. *American Journal of Respiratory Cell and Molecular Biology*,

Viral infections are associated with the majority of asthma attacks. Inhibitory M2 receptors on parasympathetic nerves, which normally limit acetylcholine (ACh) release, are dysfunctional after viral infection. Because IL-1beta is upregulated during respiratory viral infections, we investigated whether IL-1beta mediates M2 receptor dysfunction during parainfluenza virus infection. Virus infected guinea pigs were pre-treated with the IL-1beta antagonist, anakinra. In the absence of anakinra, viral infection increased bronchoconstriction in response to vagal stimulation, but not to i.v. acetylcholine, and neuronal M2 muscarinic receptors were dysfunctional. Pretreatment with anakinra prevented both virus-induced increased bronchoconstriction and M2 receptor dysfunction. Anakinra did not change smooth muscle M3 muscarinic receptor response to ACh, lung viral loads, or blood and bronchoalveolar lavage leukocyte populations. Virus infection decreased M2 receptor mRNA expression in parasympathetic ganglia extracted from infected animals, and this was prevented by blocking either IL-1beta or TNF-alpha. Treatment of SK-N-SH neuroblastoma cells or primary cultures of guinea pig parasympathetic neurons with IL-1beta directly decreased M2 receptor mRNA, and this was not synergistic with TNF-alpha treatment. Treating guinea pig trachea segment with either TNF-alpha or IL-1beta in vitro increased tracheal contractions in response to activation of airway nerves by electrical field stimulation. Blocking IL-1beta during TNF-alpha treatment prevented this hyperresponsiveness. These data show that virus induced hyperreactivity and M2 dysfunction involves both IL-1beta and TNF-alpha, likely in sequence with TNF-alpha causing production of IL-1beta.

Said, A., & Jou, J. H. (2014). Hepatitis B vaccination and screening awareness in primary care practitioners. *Hepatitis Research and Treatment*, *2014*, 373212.

Introduction. The goals of Healthy People US 2020 have called for increased screening and vaccination of high-risk groups for Hepatitis B (HBV). Methods. We performed a survey of 400 randomly chosen primary care practitioners (PCPs) in Wisconsin to assess their knowledge, attitudes, and practices regarding screening and vaccination for HBV. Results. Screening rates of patients at risk of sexual transmission were low, with 61% of respondents stating that they screen patients who had more than 1 sex partner in 6 months and 86% screening patients with a history of sex with prostitutes. Screening rate for persons with a history of intravenous drug use was 94%. Children of immigrants were screened by 65%, persons on hemodialysis by 73%, and prison inmates by 69%. Screening increased with provider experience with HBV. Deficiencies in vaccination rates mirrored screening practices. Major barriers to screening were cost, someone else's responsibility, time constraints, or lack of knowledge. Conclusions. Without improved education and practices of PCPs about HBV screening and vaccination, the goals of healthy people 2020 regarding HBV will not be met. Barriers to screening and vaccination need to be addressed. Cost-effectiveness of alternative strategies such as universal vaccination under the age of 50 should be explored.

Sanders, D. S., Read-Brown, S., Tu, D. C., Lambert, W. E., Choi, D., Almario, B. M., et al. (2014). Impact of an electronic health record operating room management system in ophthalmology on documentation time, surgical volume, and staffing. *JAMA Ophthalmology*,
IMPORTANCE Although electronic health record (EHR) systems have potential benefits, such as improved safety and quality of care, most ophthalmology practices in the United States have not adopted these systems. Concerns persist regarding potential negative impacts on clinical workflow. In particular, the impact of EHR operating room (OR) management systems on clinical efficiency in the ophthalmic surgery setting is unknown. OBJECTIVE To determine the impact of an EHR OR management system on intraoperative nursing documentation time, surgical volume, and staffing requirements. DESIGN, SETTING, AND PARTICIPANTS For documentation time and circulating nurses per procedure, a prospective cohort design was used between January 10, 2012, and January 10, 2013. For surgical volume and overall staffing requirements, a case series design was used between January 29, 2011, and January 28, 2013. This study involved ophthalmic OR nurses (n = 13) and surgeons (n = 25) at an academic medical center.

EXPOSURES Electronic health record OR management system implementation. MAIN OUTCOMES AND MEASURES (1) Documentation time (percentage of operating time documenting [POTD], absolute documentation time in minutes), (2) surgical volume (procedures/time), and (3) staffing requirements (full-time equivalents, circulating nurses/procedure). Outcomes were measured during a baseline period when paper documentation was used and during the early (first 3 months) and late (4-12 months) periods after EHR implementation. RESULTS There was a worsening in total POTD in the early EHR period (83%) vs paper baseline (41%) (P < .001). This improved to baseline levels by the late EHR period (46%, P = .28), although POTD in the cataract group remained worse than at baseline (64%, P < .001). There was a worsening in absolute mean documentation time in the early EHR period (16.7 minutes) vs paper baseline (7.5 minutes) (P < .001). This improved in the late EHR period (9.2 minutes) but remained worse than in the paper baseline (P < .001). While cataract procedures required more circulating nurses in the early EHR (mean, 1.9 nurses/procedure) and late EHR (mean, 1.5 nurses/procedure) periods than in the paper baseline (mean, 1.0 nurses/procedure) (P < .001), overall staffing requirements and surgical volume were not significantly different between the periods. CONCLUSIONS AND RELEVANCE Electronic health record OR management system implementation was associated with worsening of intraoperative nursing documentation time especially in shorter procedures. However, it is possible to implement an EHR OR management system without serious negative impacts on surgical volume and staffing requirements.

Saultz, J. (2014). Teaching excellence. *Family Medicine*, *46*(4), 311-312.

Scott, G. D., Karns, C. M., Dow, M. W., Stevens, C., & Neville, H. J. (2014). Enhanced peripheral visual processing in congenitally deaf humans is supported by multiple brain regions, including primary auditory cortex. *Frontiers in Human Neuroscience*, *8*, 177.

Brain reorganization associated with altered sensory experience clarifies the critical role of neuroplasticity in development. An example is enhanced peripheral visual processing associated with congenital deafness, but the neural systems supporting this have not been fully characterized. A gap in our understanding of deafness-enhanced peripheral vision is the contribution of primary auditory cortex. Previous studies of auditory cortex that use anatomical

normalization across participants were limited by inter-subject variability of Heschl's gyrus. In addition to reorganized auditory cortex (cross-modal plasticity), a second gap in our understanding is the contribution of altered modality-specific cortices (visual intramodal plasticity in this case), as well as supramodal and multisensory cortices, especially when target detection is required across contrasts. Here we address these gaps by comparing fMRI signal change for peripheral vs. perifoveal visual stimulation (11-15 degrees vs. 2-7 degrees ) in congenitally deaf and hearing participants in a blocked experimental design with two analytical approaches: a Heschl's gyrus region of interest analysis and a whole brain analysis. Our results using individually-defined primary auditory cortex (Heschl's gyrus) indicate that fMRI signal change for more peripheral stimuli was greater than perifoveal in deaf but not in hearing participants. Whole-brain analyses revealed differences between deaf and hearing participants for peripheral vs. perifoveal visual processing in extrastriate visual cortex including primary auditory cortex, MT+/V5, superior-temporal auditory, and multisensory and/or supramodal regions, such as posterior parietal cortex (PPC), frontal eye fields, anterior cingulate, and supplementary eye fields. Overall, these data demonstrate the contribution of neuroplasticity in multiple systems including primary auditory cortex, supramodal, and multisensory regions, to altered visual processing in congenitally deaf adults.

Sebastian, R. A., Ramos, M. M., Stumbo, S., McGrath, J., & Fairbrother, G. (2014). Measuring youth health engagement: Development of the youth engagement with health services survey. *The Journal of Adolescent Health : Official Publication of the Society for Adolescent Medicine*, PURPOSE: The purpose of this study was to create and validate a survey instrument designed to measure Youth Engagement with Health Services (YEHS!). METHODS: A 61-item YEHS! survey was created through a multistaged process, which included literature review, subject matter expert opinion, review of existing validated measures, and cognitive interviewing with 41 adolescents in Colorado and New Mexico. The YEHS! was then pilot tested with a diverse group of high school students (n = 354) accessing health services at one of eight school-based health centers in Colorado and New Mexico. We conducted psychometric analyses and examined correlations between the youth health engagement scales and measures of quality of care. RESULTS: We created scales to measure two domains of youth health engagement: health access

literacy and health self-efficacy. The youth health engagement scales demonstrated strong reliability (Cronbach's alpha .76 and .82) and construct validity (mean factor loading .71 and .76). Youth health engagement scores predicted higher experiences of care scores ($p < .001$) and receipt of more anticipatory guidance ($p < .01$). CONCLUSIONS: This study supports the YEHS! as a valid and reliable measure of youth health engagement among adolescents using school-based health centers. We demonstrate an association between youth health engagement and two quality of care measures. Additional testing is needed to ensure the reliability and validity of the instrument in diverse adolescent populations.

Shang, F., Wilmarth, P. A., Chang, M. -., Liu, K., David, L. L., Caceres, M. A., et al. (2014). Newborn mouse lens proteome and its alteration by lysine 6 mutant ubiquitin. *Journal of Proteome Research*, *13*(3), 1177-1189.

Ubiquitin is a tag that often initiates degradation of proteins by the proteasome in the ubiquitin proteasome system. Targeted expression of K6W mutant ubiquitin (K6W-Ub) in the lens results in defects in lens development and cataract formation, suggesting critical functions for ubiquitin in lens. To study the developmental processes that require intact ubiquitin, we executed the most extensive characterization of the lens proteome to date. We quantified lens protein expression changes in multiple replicate pools of P1 wild-type and K6W-Ub-expressing mouse lenses. Lens proteins were digested with trypsin, peptides were separated using strong cation exchange and reversed-phase liquid chromatography, and tandem mass (MS/MS) spectra were collected with a linear ion trap. Transgenic mice that expressed low levels of K6W-Ub (low expressers) had normal, clear lenses at birth, whereas the lenses that expressed high levels of K6W-Ub (higher expressers) had abnormal lenses and cataracts at birth. A total of 2052 proteins were identified, of which 996 were reliably quantified and compared between wild-type and K6W-Ub transgenic mice. Consistent with a delayed developmental program, fiber-cell-specific proteins, such as γ-crystallins (γA, γB, γC, and γE), were down-regulated in K6W-Ub higher expressers. Up-regulated proteins were involved in energy metabolism, signal transduction, and proteolysis. The K6W-Ub low expressers exhibited delayed onset and milder cataract consistent with smaller changes in protein expression. Because lens protein expression changes occurred prior to lens morphological abnormalities and cataract formation in K6W-Ub low expressers, it appears that expression of

K6W-Ub sets in motion a process of altered protein expression that results in developmental defects and cataract. © 2014 American Chemical Society.

Shaw, P., Stringaris, A., Nigg, J., & Leibenluft, E. (2014). Emotion dysregulation in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *171*(3), 276-293.
Although it has long been recognized that many individuals with attention deficit hyperactivity disorder (ADHD) also have difficulties with emotion regulation, no consensus has been reached on how to conceptualize this clinically challenging domain. The authors examine the current literature using both quantitative and qualitative methods. Three key findings emerge. First, emotion dysregulation is prevalent in ADHD throughout the lifespan and is a major contributor to impairment. Second, emotion dysregulation in ADHD may arise from deficits in orienting toward, recognizing, and/or allocating attention to emotional stimuli; these deficits implicate dysfunction within a striato-amygdalo-medial prefrontal cortical network. Third, while current treatments for ADHD often also ameliorate emotion dysregulation, a focus on this combination of symptoms reframes clinical questions and could stimulate novel therapeutic approaches. The authors then consider three models to explain the overlap between emotion dysregulation and ADHD: Emotion dysregulation and ADHD are correlated but distinct dimensions; emotion dysregulation is a core diagnostic feature of ADHD; and the combination constitutes a nosological entity distinct from both ADHD and emotion dysregulation alone. The differing predictions from each model can guide research on the much-neglected population of patients with ADHD and emotion dysregulation.

Sibley, C. T. (2014). Spins and loops: Linking myocardial T1 time to invasively-measured hemodynamics. *Journal of the American College of Cardiology*, *63*(11), 1119-1120.

Sittig, D. F., Ash, J. S., & Singh, H. (2014). ONC issues guides for SAFER EHRs. *Journal of the American Health Information Management Association*, *85*(4), 50-52.

Sitzmann, B. D., Brown, D. I., Garyfallou, V. T., Kohama, S. G., Mattison, J. A., Ingram, D. K., et al. (2014). Impact of moderate calorie restriction on testicular morphology and endocrine function in adult rhesus macaques (macaca mulatta). *Age*, *36*(1), 183-197.
We previously reported that moderate calorie restriction (CR) has minimal impact on testicular

gene expression in young adult rhesus macaques, and no obvious negative impact on semen quality or plasma testosterone levels. We now extend these findings by examining the influence of CR on various aspects of the reproductive axis of older males, including 24-h circulating testosterone levels, testicular gene expression, and testicular morphology. Young adult and old adult male rhesus macaques were subjected to either 30% CR for 5-7 years, or were fed a standard control diet. Analysis of the 24-h plasma testosterone profiles revealed a significant age-associated decline, but no evidence for CR-induced suppression in either the young or old males. Similarly, expression profiling of key genes associated with testosterone biosynthesis and Leydig cell maintenance showed no significant CR-induced changes in either the young or old animals. The only evidence for CR-associated negative effects on the testis was detected in the old animals at the histological level; when old CR animals were compared with their age-matched controls, there was a modest decrease in seminiferous tubule diameter and epithelium height, with a concomitant increase in the number of depleted germ cell lines. Reassuringly, data from this study and our previous study suggest that moderate CR does not negatively impact 24-h plasma testosterone profiles or testicular gene expression. Although there appear to be some minor CR-induced effects on testicular morphology in old animals, it is unclear if these would significantly compromise fertility. 

Slatore, C., Baumann, C., Pappas, M., & Humphrey, L. L. (2014). Smoking behaviors among patients receiving computed tomography for lung cancer screening: Systematic review in support of the U.S. preventive services task force. *Annals of the American Thoracic Society*,

Abstract Rationale: Lung cancer screening using low-dose computed tomography (LDCT) is now widely recommended for adults who are current or former heavy smokers. It is important to evaluate the impact of screening on smoking abstinence rates. Objective: Among current and former smokers eligible for lung cancer screening, we sought to determine the consequence of screening with LDCT, as well as subsequent results, on smoking cessation and relapse rates. Evidence Review: We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 4th Quarter 2012), MEDLINE (2000 to May 31, 2013), reference lists of papers, and Scopus for relevant English-language studies and systematic reviews. To evaluate the effect of LDCT screening on smoking abstinence, we included only

randomized controlled trials (RCT) involving asymptomatic adults. To evaluate the association of particular results and/or recommendations from a screening CT with smoking behaviors, we included results from RCTs as well cohort studies. Measurements and Main Results: A total of 8215 abstracts were reviewed. Three publications from two European RCTs and five publications from three cohort studies conducted in the U.S. met inclusion criteria. The process of LDCT lung cancer screening did not influence smoking behaviors. LDCT recipients with results concerning for lung cancer had higher abstinence rates than those with scans without such findings. This association may have a dose-response relationship in terms of the number of abnormal CT scans as well as the seriousness of the finding. Conclusions: Limited evidence suggests LDCT lung cancer screening itself does not influence smoking behaviors but positive results are associated with increased abstinence. As lung cancer screening is implemented in the general population, it is very important to evaluate its association with smoking behaviors in order to maximize its potential as a teachable moment to encourage long term abstinence. Clinicians should consider tailoring LDCT result communication to emphasize the importance of smoking abstinence.

Slee, S. J., & Young, E. D. (2014). Alignment of sound localization cues in the nucleus of the brachium of the inferior colliculus. *Journal of Neurophysiology*,

Accurate sound localization is based on three acoustic cues (interaural time and intensity difference, and spectral cues from directional filtering by the pinna). In natural listening conditions, every spatial position of a sound source provides a unique combination of these 3 cues in "natural alignment". Although neurons in the central nucleus of the inferior colliculus (ICC) are sensitive to multiple cues, they do not favor their natural spatial alignment. We tested for sensitivity to cue alignment in the nucleus of the brachium of the IC (BIN) in unanesthetized marmoset monkeys. The BIN receives its predominant auditory input from ICC and projects to the topographic auditory space map in the superior colliculus. Sound localization cues measured in each monkey were used to synthesize broadband stimuli with aligned and misaligned cues; spike responses to these stimuli were recorded in the BIN. We computed mutual information (MI) between the set of spike rates and the stimuli containing either aligned or misaligned cues. The results can be summarized as follows: 1) BIN neurons encode more information about auditory space when cues are aligned compared to misaligned. 2) Significantly more units prefer aligned

cues in the BIN than in ICC. 3) An additive model based on summing the responses to stimuli with the localization cues varying individually accurately predicts the alignment preference with all cues varying. Overall, the results suggest that the BIN is the first site in the ascending mammalian auditory system that is tuned to natural combinations of sound localization cues.

Slifka, M. K., & Amanna, I. (2014). How advances in immunology provide insight into improving vaccine efficacy. *Vaccine*,

Vaccines represent one of the most compelling examples of how biomedical research has improved society by saving lives and dramatically reducing the burden of infectious disease. Despite the importance of vaccinology, we are still in the early stages of understanding how the best vaccines work and how we can achieve better protective efficacy through improved vaccine design. Most successful vaccines have been developed empirically, but recent advances in immunology are beginning to shed new light on the mechanisms of vaccine-mediated protection and development of long-term immunity. Although natural infection will often elicit lifelong immunity, almost all current vaccines require booster vaccination in order to achieve durable protective humoral immune responses, regardless of whether the vaccine is based on infection with replicating live-attenuated vaccine strains of the specific pathogen or whether they are derived from immunization with inactivated, non-replicating vaccines or subunit vaccines. The form of the vaccine antigen (e.g., soluble or particulate/aggregate) appears to play an important role in determining immunogenicity and the interactions between dendritic cells, B cells and T cells in the germinal center are likely to dictate the magnitude and duration of protective immunity. By learning how to optimize these interactions, we may be able to elicit more effective and long-lived immunity with fewer vaccinations.

Smith, B. K., Greenberg, J. A., & Mitchell, E. L. (2014). The evolving integrated vascular surgery residency curriculum. *Annals of Vascular Surgery*,

BACKGROUND AND OBJECTIVES: Since their introduction several years ago, Integrated (0+5) Vascular Surgery Residency Programs are being increasingly developed across the country. To date, however there is no defined "universal" curriculum for these programs and each program is responsible for creating its own curriculum. The aim of this study was to review the experiences

of current 0+5 Program Directors (PD) to determine what factors contributed to the curricular development within their institution. METHODS: Semi-structured interviews were conducted with 0+5 PDs to explore their experiences with program development, factors influencing the latter, and rationale for current curricula. The interview script was loosely structured to explore several factors including: time of incoming residents first exposure to the vascular surgical service, timing and rationale behind the timing of core surgical rotations throughout the 5 year program, educational value of non-surgical rotations, opportunities for leadership and scholarly activity, and influence the general surgery program and institutional climate had on curricular structure. All interviews were conducted by a single interviewer. All interviews were qualitatively analyzed using emergent theme analysis. RESULTS: 26 0+5 PDs participated in the study. 69% believed establishing professional identity early reduces resident attrition and recommend starting incoming trainees on vascular surgical services. 62% spread core surgical rotations over the 1st three years to optimize general surgical exposure and the majority of programs have eliminated specific rotations as they were not considered valuable to the goals of training. Factors considered most important by PDs in curricular development include: building upon existing institutional opportunities (96%), avoiding rotations considered unsuccessful by "experienced" programs (92%), and maintaining a good working relationship with general surgery (77 %). 58% of PDs voiced concern over the lack of standardization amongst the differing programs and the majority of PDs agree that some degree of programmatic standardization is critical for the continued success of the 0+5 training paradigm. CONCLUSIONS: Qualitative evaluation of PD experiences with the development of 0+5 vascular surgery residency programs reveals the key factors that commonly influence program design. Programs continue to evolve in both structure and content as PDs respond to these influences. Learning from the collective experience of PDs and some standardization of the curricula may help current and future programs avoid common pitfalls in curricular development.

Snowden, J. M., Wei, C., McFarland, W., & Raymond, H. F. (2014). Prevalence, correlates and trends in seroadaptive behaviours among men who have sex with men from serial cross-sectional surveillance in san francisco, 2004-2011. *Sexually Transmitted Infections,*

OBJECTIVES: We sought to assess the prevalence and correlates of seroadaptive behaviours (ie,

sexual history incorporating some unprotected anal intercourse (UAI)) and conventional risk reduction behaviours (ie, consistent condom use or no anal intercourse) among men who have sex with men (MSM) in San Francisco in 2011. We compared the prevalence of seroadaptive behaviours between serial cross-sectional surveys from 2004, 2008 and 2011. METHODS: We analysed data from the 2011 wave of the National HIV Behavioral Surveillance system in San Francisco. We categorised men's self-reported sexual behaviour history in the past 6 months into a schema of seroadaptive behaviours and conventional risk reduction behaviours. We compared the prevalence of behaviour categories by self-reported HIV serostatus, HIV testing history, awareness of pre-exposure HIV prophylaxis (PrEP) and diagnosis of a sexually transmitted infection (STI). RESULTS: Seroadaptive behaviours remained common in San Francisco MSM, with a 2011 prevalence of 46.6%, up from 35.9% in 2004. Consistent condom use or no anal intercourse was more common than seroadaptive behaviours in HIV-negative MSM, men who had not heard of PrEP and men without an STI diagnosis. Seroadaptive behaviours increased from 2004 to 2011. CONCLUSIONS: HIV seroadaptive behaviours remain common in San Francisco MSM, have increased in the last decade and are practiced differently by MSM with different sexual health knowledge and outcomes. Public health researchers and officials should continue to document the prevalence, intentionality, efficacy and safety of seroadaptive behaviours among diverse communities of MSM.

Soot, L., Weerasinghe, R., Wang, L., & Nelson, H. D. (2014). Rates and indications for surgical breast biopsies in a community-based health system. *American Journal of Surgery, 207*(4), 499-503. Background High rates of surgical breast biopsies in community hospitals have been reported but may misrepresent actual practice. Methods Patient-level data from 5,757 women who underwent breast biopsies in a large integrated health system were evaluated to determine biopsy types, rates, indications, and diagnoses. Results Between 2008 and 2010, 6,047 breast biopsies were performed on 5,757 women. Surgical biopsy was the initial diagnostic procedure in 16% (n = 942) of women overall and in 6% (72 of 1,236) of women with newly diagnosed invasive breast cancer. Invasive breast cancer was diagnosed in 72 women (8%) undergoing surgical biopsy compared with 1,164 (24%) undergoing core needle biopsy (P <.001, age adjusted). Main indications for surgical biopsies included symptomatic abnormalities, technical challenges, and

patient choice. Conclusions Surgical biopsy was the initial diagnostic procedure in 16% of women with breast abnormalities, comparable with rates at academic centers. Rates could be improved by more careful consideration of indications. © 2014 Elsevier Inc. All rights reserved.

Spiros, A., Roberts, P., & Geerts, H. (2013). Phenotypic screening of the prestwick library for treatment of parkinson's tremor symptoms using a humanized quantitative systems pharmacology platform. *Journal of Parkinson's Disease, 3*(4), 569-580.
Background: Possible solutions for the low success rate in CNS Drug discovery and development in CNS diseases include drug repurposing. Objectives: As a possible alternative to prohibitively expensive systematic testing in animal models, we propose to use a humanized quantitative systems pharmacology (QSP) platform as an example of a well-validated phenotypic assay in Parkinson's disease (PD) tremor for filtering out possible interesting molecules that then can be tested in preclinical animal models. This will significantly reduce discovery time and costs, while at the same time providing a better predictability to the human clinical outcome. The method will be applied to the Prestwick library, a library of FDA approved and off-patent medications. Methods: The platform contains 30 CNS physiologically implemented targets and simulates biophysically realistic neuronal network interactions between supplemental motor cortex and motor striatum based on preclinical neurophysiology and human electrophysiology data. Importantly, the platform is further calibrated using retrospective clinical data on Parkinsonian side-effects with antipsychotics. Results: We use this QSP platform to screen pharmacological profiles of serotonergic drugs in the Prestwick library. We identified five interesting multi-pharmacology agents, including trazodone that in a previously reported study improved clinical PD scales as augmentation strategy. Conclusion: The Quantitative Systems Pharmacology platform is a powerful modeling and simulation tool with a relevant human clinical scale as output, where multi-target drugs effect can be simulated and promising candidates for further study in pharmacological profiling or animal models can be identified. © 2013 -IOS Press and the authors.

Starrels, J. L., Wu, B., Peyser, D., Fox, A. D., Batchelder, A., Barg, F. K., et al. (2014). It made my life a little easier: Primary care providers' beliefs and attitudes about using opioid treatment

agreements. *Journal of Opioid Management*, *10*(2), 95-102.

OBJECTIVE: To understand primary care providers (PCPs)' experiences, beliefs, and attitudes about using opioid treatment agreements (OTAs) for patients with chronic pain. DESIGN: Qualitative research study. PARTICIPANTS: Twenty-eight internists and family medicine physicians at two health centers. APPROACH: Semistructured telephone interviews, informed by the Integrative Model of Behavioral Prediction. Themes were analyzed using a Grounded Theory approach, and similarities and differences in themes were examined among OTA adopters, nonadopters, and selective adopters. RESULTS: Participants were 64 percent female and 68 percent white, and practiced for a mean of 9.5 years. Adoption of OTAs varied: seven were adopters, five were nonadopters, and 16 were selective adopters. OTA adoption reflected PCPs' beliefs and attitudes in the following three thematic categories: 1) perceived effect of OTA use on the therapeutic alliance, 2) beliefs about the utility of OTAs for patients or providers, and 3) perception of patients' risk for opioid misuse. PCPs commonly believed that OTAs were useful for physician self-protection, but few believed that they prevent opioid misuse. Selective adopters expressed ambivalent beliefs and made decisions about OTA use for individual patients based on both observed data and a subjective sense of each patient's risk for misuse. CONCLUSIONS: Substantial variability in PCP use of OTAs reflects differences in PCP beliefs and attitudes. Research to understand the impact of OTA use on providers, patients, and the therapeutic alliance is urgently needed to guide best practices.

Stokbro, K., Aagaard, E., Torkov, P., Bell, R. B., & Thygesen, T. (2014). Virtual planning in orthognathic surgery. *International Journal of Oral and Maxillofacial Surgery*,

Numerous publications regarding virtual surgical planning protocols have been published, most reporting only one or two case reports to emphasize the hands-on planning. None have systematically reviewed the data published from clinical trials. This systematic review analyzes the precision and accuracy of three-dimensional (3D) virtual surgical planning of orthognathic procedures compared with the actual surgical outcome following orthognathic surgery reported in clinical trials. A systematic search of the current literature was conducted to identify clinical trials with a sample size of more than five patients, comparing the virtual surgical plan with the actual surgical outcome. Search terms revealed a total of 428 titles, out of which only seven articles

were included, with a combined sample size of 149 patients. Data were presented in three different ways: intra-class correlation coefficient, 3D surface area with a difference <2mm, and linear and angular differences in three dimensions. Success criteria were set at 2mm mean difference in six articles; 125 of the 133 patients included in these articles were regarded as having had a successful outcome. Due to differences in the presentation of data, meta-analysis was not possible. Virtual planning appears to be an accurate and reproducible method for orthognathic treatment planning. A more uniform presentation of the data is necessary to allow the performance of a meta-analysis. Currently, the software system most often used for 3D virtual planning in clinical trials is SimPlant (Materialise). More independent clinical trials are needed to further validate the precision of virtual planning.

Sullivan, D. R., Ganzini, L., Lopez-Chavez, A., & Slatore, C. G. (2014). Association of patient characteristics with chemotherapy receipt among depressed and non-depressed patients with non-small cell lung cancer. *Psycho-Oncology*,

Takahashi, C. E., Brambrink, A. M., Aziz, M. F., Macri, E., Raines, J., Multani-Kohol, A., et al. (2014). Association of intraprocedural blood pressure and end tidal carbon dioxide with outcome after acute stroke intervention. *Neurocritical Care*, *20*(2), 202-208.

Background: General anesthesia (GA) for acute stroke interventions may be associated with inferior functional outcomes. Our goal was to identify physiologic parameters that mediate this association. Methods: Consecutive patients treated at our institution between August 2007 and December 2010 were identified from a prospective database. Clinical data were then extracted by retrospective chart review. Variables significantly associated with outcome in univariate analysis were also examined in multivariate analysis, controlling for well-established prespecified predictors of functional outcome. Results: Of the 106 patients identified, 20 were excluded (17 due to the absence of 90-day mRS and 3 due to insufficient anesthetic records). Blood pressure (BP) decreased significantly after induction of GA, but there was no association between BP and outcome. End tidal carbon dioxide values (ETCO2) at 60 and 90 min, however, were significantly associated with outcomes in both univariate and multivariate analyses. Mean ETCO2 in patients with favorable outcomes (modified Rankin Scale (mRS) 0-3) was higher than in those with

unfavorable outcomes (mRS 4-6): 35.2 mmHg versus 32.2 (p = 0.03) at 60 min and 34.9 versus 31.9 (p = 0.04) at 90 min. The adjusted odds ratios for poor outcomes for each 1 mmHg decrease in ETCO2 were the same: 0.76 (95 % CI 0.65-0.92; p = 0.004) at 60 min and 0.76 (95 % CI 0.61-0.93; p = 0.01) at 90 min. Conclusions: While BP decreased significantly in patients undergoing GA for acute stroke intervention, it did not correlate with patient outcome. Decreases in ETCO2 at 30 and 60 min, however, were associated with 90-day mRS. © 2013 Springer Science+Business Media.

Tan, W. C., Bourbeau, J., Hernandez, P., Chapman, K. R., Cowie, R., FitzGerald, J. M., et al. (2014). Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: Results from a population-based study. *Thorax*,

Rationale: Exacerbations of COPD are defined clinically by worsening of chronic respiratory symptoms. Chronic respiratory symptoms are common in the general population. There are no data on the frequency of exacerbation-like events in individuals without spirometric evidence of COPD. Aims: To determine the occurrence of 'exacerbation-like' events in individuals without airflow limitation, their associated risk factors, healthcare utilisation and social impacts. Method: We analysed the cross-sectional data from 5176 people aged 40 years and older who participated in a multisite, population-based study on lung health. The study cohort was stratified into spirometrically defined COPD (post-bronchodilator FEV1/FVC<0.7) and non-COPD (post bronchodilator FEV1/FVC≥0.7 and without self-reported doctor diagnosis of airway diseases) subgroups and then into those with and without respiratory 'exacerbation-like' events in the past year. Results: Individuals without COPD had half the frequency of 'exacerbation-like' events compared with those with COPD. In the non-COPD group, the independent associations with 'exacerbations' included female gender, presence of wheezing, the use of respiratory medications and self-perceived poor health. In the non-COPD group, those with exacerbations were more likely than those without exacerbations to have poorer health-related quality of life (12-item Short-Form Health Survey), miss social activities (58.5% vs 18.8%), miss work for income (41.5% vs 17.3%) and miss housework (55.6% vs 16.5%), p<0.01 to <0.0001. Conclusions: Events similar to exacerbations of COPD can occur in individuals without COPD or asthma and are associated with significant health and socioeconomic outcomes. They increase the respiratory

burden in the community and may contribute to the false-positive diagnosis of asthma or COPD. © 2014 BMJ Publishing Group Ltd & British Thoracic Society.

Tan, W. C., Bourbeau, J., O'donnell, D., Aaron, S., Maltais, F., Marciniuk, D., et al. (2014). Quality assurance of spirometry in a population-based study-predictors of good outcome in spirometry testing. *COPD: Journal of Chronic Obstructive Pulmonary Disease*, *11*(2), 143-151.

Background: The assurance of high-quality spirometry testing remains a challenge. Methods: Spirometry training consisted of standardized coaching followed by certification for 35 spirometry-naïve and 9 spirometry-experienced research assistants. Spirometry was performed before and after bronchodilator (BD) in random population samples of 5176 people aged 40 years and older from 9 sites in Canada. using the hand-held EasyOne spirometer (ndd Medical Technologies Inc., Andover, MA, USA). Pulmonary function quality assurance with over reading was conducted centrally in Vancouver: spirograms were reviewed and graded according to ATS/ERS standards with prompt feedback to the technician at each site. Descriptive statistics were calculated for manoeuvre acceptability and repeatability variables. A logistic regression model was constructed for the predictors of spirometry quality success. Results: 95% of test sessions achieved pre-determined quality standards for back extrapolated volume (BEV), time to peak flow (PEFT) and end of test volume (EOTV). The mean forced expiratory time (FET) was 11.2 seconds. Then, 90% and 95% of all manoeuvres had FEV1 and FVC that were repeatable within 150 ml and 200 ml respectively. Test quality was slightly better for post-BD test sessions compared with pre-BD for both groups of research assistants. Independent predictors of acceptable test quality included participant characteristics: female sex, younger age, greater BD responsiveness; but not study site or prior experience in completing spirometry by the technologist. Conclusions: Good quality spirometry tests are attainable in large multicenter epidemiological studies by trained research assistants, irrespective of their prior experience in spirometry. © 2014 Informa Healthcare USA, Inc.

Tarlow, B. D., Finegold, M. J., & Grompe, M. (2014). Clonal tracing of Sox9+ liver progenitors in oval cell injury. *Hepatology (Baltimore, Md.)*,

Proliferating ducts, termed "oval cells", have long thought to be bipotential, i.e. produce both

biliary ducts and hepatocytes during chronic liver injury. The precursor to oval cells is considered to be a facultative liver stem cell (LSC). Recent lineage tracing experiments indicated that the LSC is Sox9+ and can replace the bulk of hepatocyte mass in several settings. However, no clonal relationship between Sox9+ cells and the two epithelial liver lineages was established. We labeled Sox9+ mouse liver cells at low density with a multicolor fluorescent confetti reporter. Organoid formation validated the progenitor activity of the labeled population. Sox9+ cells were traced in multiple oval cell injury models using both histology and FACS. Surprisingly, only rare clones containing both hepatocytes and oval cells were found in any experiment. Quantitative analysis showed that Sox9+ cells contributed only minimally (<1%) to the hepatocyte pool, even in classic oval cell injury models. In contrast, clonally marked mature hepatocytes demonstrated the ability to self-renew in all classic mouse oval cell activation injuries. A hepatocyte chimera model to trace hepatocytes and non-parenchymal cells also demonstrated the prevalence of hepatocyte-driven regeneration in mouse oval cell injury models. Conclusion: Sox9+ ductal progenitor cells give rise to clonal oval cell proliferation and bipotential organoids but rarely produce hepatocytes in vivo. Hepatocytes themselves are the predominant source of new parenchyma cells in prototypical mouse models of oval cell activation. (Hepatology 2014;).

Taylor, K. R., Mackay, A., Truffaux, N., Butterfield, Y. S., Morozova, O., Philippe, C., et al. (2014). Recurrent activating ACVR1 mutations in diffuse intrinsic pontine glioma. *Nature Genetics, 46*(5), 457-461.

Diffuse intrinsic pontine gliomas (DIPGs) are highly infiltrative malignant glial neoplasms of the ventral pons that, due to their location within the brain, are unsuitable for surgical resection and consequently have a universally dismal clinical outcome. The median survival time is 9-12 months, with neither chemotherapeutic nor targeted agents showing substantial survival benefit in clinical trials in children with these tumors. We report the identification of recurrent activating mutations in the ACVR1 gene, which encodes a type I activin receptor serine/threonine kinase, in 21% of DIPG samples. Strikingly, these somatic mutations (encoding p.Arg206His, p.Arg258Gly, p.Gly328Glu, p.Gly328Val, p.Gly328Trp and p.Gly356Asp substitutions) have not been reported previously in cancer but are identical to mutations found in the germ line of individuals with the congenital childhood developmental disorder fibrodysplasia ossificans progressiva (FOP) and have

been shown to constitutively activate the BMP-TGF-beta signaling pathway. These mutations represent new targets for therapeutic intervention in this otherwise incurable disease.

Thompson, E. M., Baird, L. C., & Selden, N. R. (2014). Results of a north american survey of rapid-sequence MRI utilization to evaluate cerebral ventricles in children. *Journal of Neurosurgery.Pediatrics*,

Object Growing concern about potential adverse effects of ionizing radiation exposure during imaging studies is particularly relevant to the pediatric population. To decrease radiation exposure, many institutions use rapid-sequence (or quick-brain) MRI to evaluate cerebral ventricle size. There are obstacles, however, to widespread implementation of this imaging modality. The purpose of this study was to define and quantify these obstacles to positively affect institutional and governmental policy. Methods A 9-question survey was emailed to pediatric neurosurgeons who were either members or candidate members of the American Society of Pediatric Neurosurgeons at every one of 101 institutions in the US and Canada having such a neurosurgeon on staff. Responses were compiled and descriptive statistics were performed. Results Fifty-six institutions completed the survey. Forty-four (79%) of the 56 institutions currently have a rapid-sequence MRI protocol to evaluate ventricle size, while 36 (64%) use it routinely. Of the 44 institutions with a rapid-sequence MRI protocol, 29 (66%) have had a rapid-sequence MRI protocol for less than 5 years while 39 (89%) have had a rapid-sequence MRI protocol for no more than 10 years. Thirty-six (88%) of 41 rapid-sequence MRI users responding to this question obtain a T2-weighted rapid-sequence MRI while 13 (32%) obtain a T1-weighted rapid-sequence MRI. Twenty-eight (64%) of 44 institutions never use sedation while an additional 12 (27%) rarely use sedation to obtain a rapid-sequence MRI (less than 5% of studies). Of the institutions with an established rapid-sequence MRI protocol, obstacles to routine use include lack of emergency access to MRI facilities in 18 (41%), lack of staffing of MRI facilities in 12 (27%), and the inability to reimburse a rapid-sequence MRI protocol in 6 (14%). In the 12 institutions without rapid-sequence MRI, obstacles to implementation include lack of emergency access to MRI facilities in 8 (67%), lack of staffing of MRI facilities in 7 (58%), the inability to reimburse in 3 (25%), and lack of administrative support in 3 (25%). To evaluate pediatric head trauma, 53 (96%) of 55 institutions responding to this question use noncontrast CT, no institution uses

rapid-sequence MRI, and only 2 (4%) use standard MRI. Conclusions Many North American institutions have a rapid-sequence MRI protocol to evaluate ventricle size, with most developing this technique within the past 5 years. Most institutions never use sedation, and most obtain T2-weighted sequences. The greatest obstacles to the routine use of rapid-sequence MRI in institutions with and in those without a rapid-sequence MRI protocol are the lack of emergency access and staffing of the MRI facility during nights and weekends.

Totonchy, J. E., Clepper, L., Phillips, K. G., McCarty, O. J., & Moses, A. V. (2014). CXCR7 expression disrupts endothelial cell homeostasis and causes ligand-dependent invasion. *Cell Adhesion & Migration, 8*(2)

The homeostatic function of endothelial cells (EC) is critical for a number of physiological processes including vascular integrity, immunity, and wound healing. Indeed, vascular abnormalities resulting from EC dysfunction contribute to the development and spread of malignancies. The alternative SDF-1/CXCL12 receptor CXCR7 is frequently and specifically highly expressed in tumor-associated vessels. In this study, we investigate whether CXCR7 contributes to vascular dysfunction by specifically examining the effect of CXCR7 expression on EC barrier function and motility. We demonstrate that CXCR7 expression in EC results in redistribution of CD31/PECAM-1 and loss of contact inhibition. Moreover, CXCR7+ EC are deficient in barrier formation. We show that CXCR7-mediated motility has no influence on angiogenesis but contributes to another motile process, the invasion of CXCR7+ EC into ligand-rich niches. These results identify CXCR7 as a novel manipulator of EC barrier function via alteration of PECAM-1 homophilic junctions. As such, aberrant expression of CXCR7 in the vasculature has the potential to disrupt vascular homeostasis and could contribute to vascular dysfunction in cancer systems.

Tritos, N. A., Johannsson, G., Korbonits, M., Miller, K. K., Feldt-Rasmussen, U., Yuen, K. C., et al. (2014). Effects of long-term growth hormone replacement in adults with growth hormone deficiency following cure of acromegaly: A KIMS analysis. *The Journal of Clinical Endocrinology and Metabolism, ,* jc20141013.

Context: GH deficiency (GHD) may occur in adults with cured acromegaly (acroGHD). Objective: Our objective was to examine the effectiveness and safety of GH replacement in acroGHD.

Design: This study was a retrospective analysis of data from KIMS (Pfizer International Metabolic Database). Setting: We conducted a pharmaco-epidemiological survey of >16 000 GHD adults from 31 countries. Patients: The effectiveness population included 115 adults with acroGHD and 142 age-, gender-, and body mass index-matched GHD adults with nonfunctioning pituitary adenoma (NFPA) followed up to 5 years on GH. The Safety population included 164 adults with acroGHD and 2469 with NFPA, all GH-replaced. Both acroGHD and NFPA were compared with several cohorts from the general population (including the World Health Organization Global Burden of Disease). Outcome Measures: Outcome measures included quality of life (QoL-AGHDA), lipids, serious adverse events, and additional safety endpoints. Results: Median GH dose was 0.3 mg/d in acroGHD and NFPA at 5 years. There were comparable improvements in QoL-AGHDA and total and low-density lipoprotein cholesterol in acroGHD and NFPA. High-density lipoprotein cholesterol increased only in acroGHD. Cardiovascular mortality was increased in acroGHD vs NFPA (standardized mortality ratio = 3.03, P = .02). All-cause mortality was similar in acroGHD (ratio between observed/expected cases [95% confidence interval] = 1.32 [0.70-2.25]) and lower in NFPA [observed/expected = 0.58 [0.48-0.70]) in comparison with the general population. There was no difference in incidence of all cancers, benign or malignant brain tumors, or diabetes mellitus between acroGHD and NFPA. Conclusions: GH replacement has comparable effects on quality of life and lipids in acroGHD and NFPA. Further investigation is needed to examine whether the increased cardiovascular mortality may be attributed to the history of previous GH excess in acroGHD.

Tseng, B. P., Giedzinski, E., Izadi, A., Suarez, T., Lan, M. L., Tran, K. K., et al. (2014). Functional consequences of radiation-induced oxidative stress in cultured neural stem cells and the brain exposed to charged particle irradiation. *Antioxidants and Redox Signaling, 20*(9), 1410-1422. Aims: Redox homeostasis is critical in regulating the fate and function of multipotent cells in the central nervous system (CNS). Here, we investigated whether low dose charged particle irradiation could elicit oxidative stress in neural stem and precursor cells and whether radiation-induced changes in redox metabolism would coincide with cognitive impairment. Results: Low doses (<1 Gy) of charged particles caused an acute and persistent oxidative stress. Early after (<1 week) irradiation, increased levels of reactive oxygen and nitrogen species were generally

dose responsive, but were less dependent on dose weeks to months thereafter. Exposure to ion fluences resulting in less than one ion traversal per cell was sufficient to elicit radiation-induced oxidative stress. Whole body irradiation triggered a compensatory response in the rodent brain that led to a significant increase in antioxidant capacity 2 weeks following exposure, before returning to background levels at week 4. Low dose irradiation was also found to significantly impair novel object recognition in mice 2 and 12 weeks following irradiation. Innovation: Data provide evidence that acute exposure of neural stem cells and the CNS to very low doses and fluences of charged particles can elicit a persisting oxidative stress lasting weeks to months that is associated with impaired cognition. Conclusions: Exposure to low doses of charged particles causes a persistent oxidative stress and cognitive impairment over protracted times. Data suggest that astronauts subjected to space radiation may develop a heightened risk for mission critical performance decrements in space, along with a risk of developing long-term neurocognitive sequelae. Antioxid. 

Tuepker, A., Kansagara, D., Skaperdas, E., Nicolaidis, C., Joos, S., Alperin, M., et al. (2014). "We've not gotten even close to what we want to do": A qualitative study of early patient-centered medical home implementation. *Journal of General Internal Medicine*,

BACKGROUND The Veterans Health Administration (VA) Patient Aligned Care Teams (PACT) initiative is designed to deliver a medical home model of care associated with better patient outcomes, but success will depend in part on the model's acceptability and sustainability among clinic employees. OBJECTIVE We sought to identify key themes in the experience of primary care providers, nurse care managers, clerical and clinical associates, and clinic administrators implementing PACT, with the aim of informing recommendations for continued development of the model and its components. DESIGN Observational qualitative study; data collection from 2010 to 2013, using role-stratified and team focus groups and semi-structured interviews. PARTICIPANTS 241 of 337 (72 %) identified primary care clinic employees in PACT team or administrative roles, from 15 VA clinics in Oregon and Washington. APPROACH Data coded and analyzed using conventional content analysis techniques. KEY RESULTS Overall, participants were enthusiastic about the PACT concept, but felt necessary resources for success were not yet in place. Well-functioning teams were perceived as key to successful implementation. Development

of such teams depended on adequate staffing, training, and dedicated time for team development. Changes within the broader VA system were also seen as necessary, including devolving greater control to the clinic level and improving system alignment with the PACT model. PACT advocates from among clinic and institutional level leadership were identified as a final key ingredient for success. These themes were consistent despite differences in clinic settings and characteristics. CONCLUSIONS PACT implementation faced significant challenges in its early years. Realizing PACT's transformative potential will require acting on the needs identified by clinic workers in this study: ensuring adequate staffing in all team roles, devoting resources to in-depth training for all employees in communication and other skills needed to maximize team success, and aligning the broader VA hospital system with PACT's decentralized, team-based approach. © 2013 Society of General Internal Medicine.

van der Heijde, D., Deodhar, A., Braun, J., Mack, M., Hsu, B., Gathany, T. A., et al. (2014). The effect of golimumab therapy on disease activity and health-related quality of life in patients with ankylosing spondylitis: 2-year results of the GO-RAISE trial. *The Journal of Rheumatology*, OBJECTIVE: To evaluate the effects of golimumab therapy on achieving inactive disease or major improvement, as assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS), and improvements in health-related quality of life (HRQOL) and productivity through 2 years in patients with AS. METHODS: In the phase III GO-RAISE trial, 356 patients were randomized to placebo with crossover to golimumab 50 mg at Week 24 (n = 78), golimumab 50 mg (n = 138), or golimumab 100 mg (n = 140) at baseline and every 4 weeks. The proportions of patients with ASDAS major improvement (improvement >/= 2.0) or inactive disease (score /= 50). The effect of disease on productivity was assessed by visual analog scale (0-10). Regression analyses on the association of disease activity and HRQOL were performed. The final assessment was at Week 104. RESULTS: Significantly greater proportions of golimumab-treated patients achieved ASDAS major improvement or inactive disease at weeks 14 and 24 versus placebo. Through Week 104, patients who achieved ASDAS inactive disease or major improvement had significantly greater improvements in SF-36 PCS and MCS scores and productivity than did patients not meeting these targets. Among all patients, achieving ASDAS inactive disease at weeks 52 and 104 was associated with normalized SF-36 PCS/MCS scores and significant improvements in work

productivity. CONCLUSION: Greater proportions of golimumab-treated patients achieved ASDAS major improvement or inactive disease and improved HRQOL versus placebo. Achieving an inactive disease state by ASDAS criteria (< 1.3) was associated with normalized HRQOL through 2 years.

Vedala, K., Motahari, S. M. A., Goryawala, M., Cabrerizo, M., Yaylali, I., & Adjouadi, M. (2013). Novel time-frequency-eigen filter for intraoperative neurophysiologic monitoring in spinal surgeries. *2013 6th International IEEE EMBS Conference on Neural Engineering, NER 2013,* San Diego, CA. pp. 1578-1581.

We present a novel signal-processing algorithm to extract the posterior tibial somatosensory evoked potentials (tSSEP) using a minimum number of trials. We analyze the proposed algorithm and compare it with the clinically used conventional signal averaging method for 12 surgical procedures. The tSSEP trials are continuously fed to our processing algorithm that displays the extracted SSEP after processing 12 successive unrejected sweeps. A unique filtering process employing time, frequency and eigen systems, in that order, was used to extract the SSEP from this set of 12 trials. The algorithm then detects, marks and records the P37 and N45 peaks using the first order differentials obtained through Walsh transformation. The monitoring using the algorithm was successful and proved conclusive to the clinical information through the different surgical procedures. Higher accuracy and faster execution time in determining the SSEP signals provides for a much improved and effective neurophysiological monitoring process. © 2013 IEEE.

Vermehren-Schmaedick, A., Krueger, W., Jacob, T., Ramunno-Johnson, D., Balkowiec, A., Lidke, K. A., et al. (2014). Heterogeneous intracellular trafficking dynamics of brain-derived neurotrophic factor complexes in the neuronal soma revealed by single quantum dot tracking. *PloS One, 9*(4), e95113.

Accumulating evidence underscores the importance of ligand-receptor dynamics in shaping cellular signaling. In the nervous system, growth factor-activated Trk receptor trafficking serves to convey biochemical signaling that underlies fundamental neural functions. Focus has been placed on axonal trafficking but little is known about growth factor-activated Trk dynamics in the neuronal soma, particularly at the molecular scale, due in large part to technical hurdles in

observing individual growth factor-Trk complexes for long periods of time inside live cells. Quantum dots (QDs) are intensely fluorescent nanoparticles that have been used to study the dynamics of ligand-receptor complexes at the plasma membrane but the value of QDs for investigating ligand-receptor intracellular dynamics has not been well exploited. The current study establishes that QD conjugated brain-derived neurotrophic factor (QD-BDNF) binds to TrkB receptors with high specificity, activates TrkB downstream signaling, and allows single QD tracking capability for long recording durations deep within the soma of live neurons. QD-BDNF complexes undergo internalization, recycling, and intracellular trafficking in the neuronal soma. These trafficking events exhibit little time-synchrony and diverse heterogeneity in underlying dynamics that include phases of sustained rapid motor transport without pause as well as immobility of surprisingly long-lasting duration (several minutes). Moreover, the trajectories formed by dynamic individual BDNF complexes show no apparent end destination; BDNF complexes can be found meandering over long distances of several microns throughout the expanse of the neuronal soma in a circuitous fashion. The complex, heterogeneous nature of neuronal soma trafficking dynamics contrasts the reported linear nature of axonal transport data and calls for models that surpass our generally limited notions of nuclear-directed transport in the soma. QD-ligand probes are poised to provide understanding of how the molecular mechanisms underlying intracellular ligand-receptor trafficking shape cell signaling under conditions of both healthy and dysfunctional neurological disease models.

Vetto, J. T. (2014). Short and sweet: A short course on concise medical writing. *Journal of Cancer Education, 29*(1), 194-195.

Vilar, L., Fleseriu, M., & Bronstein, M. D. (2014). Challenges and pitfalls in the diagnosis of hyperprolactinemia. *Arquivos Brasileiros De Endocrinologia e Metabologia, 58*(1), 9-22.
The definition of the etiology of hyperprolactinemia often represents a great challenge and an accurate diagnosis is paramount before treatment. Although prolactin levels > 200-250 ng/mL are highly suggestive of prolactinomas, they can occasionally be found in other conditions. Moreover, as much as 25% of patients with microprolactinomas may present prolactin levels < 100 ng/mL, which are found in most patients with pseudoprolactinomas, drug-induced

hyperprolactinemia, or systemic diseases. On the other hand, some conditions may lead to falsely low PRL levels, particularly the so-called hook effect, that is an assay artifact caused by an extremely high level of PRL, and can be confirmed by repeating assay after a 1:100 serum sample dilution. The hook effect must be considered in all patients with large pituitary adenomas and PRL levels within the normal range or only modestly elevated (e.g., < 200 ng/mL). An overlooked hook effect may lead to incorrect diagnosis and unnecessary surgical intervention in patients with prolactinomas. Another important challenge is macroprolactinemia, a common finding that needs to be identified, as it usually requires no treatment. Although most macroprolactinemic patients are asymptomatic, many of them may present galactorrhea or menstrual disorders, as well as neuroradiological abnormalities, due to the concomitance of other diseases. Finally, physicians should be aware that pituitary incidentalomas are found in at least 10% of adult population. Arq Bras Endocrinol Metab. 2014;58(1):9-22.

Wahbeh, H., Senders, A., Neuendorf, R., & Cayton, J. (2014). Complementary and alternative medicine for posttraumatic stress disorder symptoms: A systematic review. *Journal of Evidence-Based Complementary & Alternative Medicine*,

Objectives.To (1) characterize complementary and alternative medicine studies for posttraumatic stress disorder symptoms, (2) evaluate the quality of these studies, and (3) systematically grade the scientific evidence for individual CAM modalities for posttraumatic stress disorder.Design.Systematic review. Eight data sources were searched. Selection criteria included any study design assessing posttraumatic stress disorder outcomes and any complementary and alternative medicine intervention. The body of evidence for each modality was assessed with the Natural Standard evidence-based, validated grading rationale.Results and Conclusions.Thirty-three studies (n = 1329) were reviewed. Scientific evidence of benefit for posttraumatic stress disorder was strong for repetitive transcranial magnetic stimulation and good for acupuncture, hypnotherapy, meditation, and visualization. Evidence was unclear or conflicting for biofeedback, relaxation, Emotional Freedom and Thought Field therapies, yoga, and natural products. Considerations for clinical applications and future research recommendations are discussed.

Wang, Y., Jia, J., Ao, G., Hu, L., Liu, H., Xiao, Y., et al. (2014). Hydrogen sulfide protects blood-brain barrier integrity following cerebral ischemia. *Journal of Neurochemistry*,

By using two structurally unrelated hydrogen sulfide (H2S) donors 5-(4-methoxyphenyl) -3H-1, 2-dithiole-3-thione (ADT) and sodium hydrosulfide (NaHS), this study investigated if H2S protected blood-brain barrier (BBB) integrity following middle cerebral artery occlusion (MCAO). ICR mice underwent MCAO and received H2S donors at 3 h after reperfusion. Infarction, neurological scores, brain edema, Evans blue (EB) extravasation, and tight junction protein expression were examined at 48 h after MCAO. We also investigated if ADT protected BBB integrity by suppressing post-ischemic inflammation-induced Matrix Metalloproteimase-9 (MMP9) and Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX). ADT increased blood H2S concentrations, decreased infarction, and improved neurological deficits. Particularly, ADT reduced EB extravasation, brain edema and preserved expression of tight junction proteins in the ischemic brain. NaHS also increased blood H2S levels and reduced EB extravasation following MCAO. Moreover, ADT inhibited expression of pro-inflammatory markers induced Nitric Oxide Synthase (iNOS) and IL-1β while enhanced expression of anti-inflammatory markers arginase 1 and IL-10 in the ischemic brain. Accordingly, ADT attenuated ischemia-induced expression and activity of MMP9. Moreover, ADT reduced NOX-4 mRNA expression, NOX activity, and inhibited nuclear translocation of Nuclear Factor Kappa-B (NF-κB) in the ischemic brain. In conclusion, H2S donors protected BBB integrity following experimental stroke possibly by acting through NF-κB inhibition to suppress neuroinflammation induction of MMP9 and NOX4-derived free radicals. © 2014 International Society for Neurochemistry.

Warburton, C. (2014). 2013 november military issue. *Journal of Emergency Nursing: JEN : Official Publication of the Emergency Department Nurses Association*,

Watson, M., Benard, V., Thomas, C., Brayboy, A., Paisano, R., & Becker, T. (2014). Cervical cancer incidence and mortality among american indian and alaska native women, 1999-2009. *American Journal of Public Health*,

Objectives. We analyzed cervical cancer incidence and mortality data in American Indian and Alaska Native (AI/AN) women compared with women of other races. Methods. We improved

identification of AI/AN race, cervical cancer incidence, and mortality data using Indian Health Service (IHS) patient records; our analyses focused on residents of IHS Contract Health Service Delivery Area (CHSDA) counties. Age-adjusted incidence and death rates were calculated for AI/AN and White women from 1999 to 2009. Results. AI/AN women in CHSDA counties had a death rate from cervical cancer of 4.2, which was nearly twice the rate in White women (2.0; rate ratio [RR] = 2.11). AI/AN women also had higher incidence rates of cervical cancer compared with White women (11.0 vs 7.1; RR = 1.55) and were more often diagnosed with later-stage disease (RR = 1.84 for regional stage and RR = 1.74 for distant stage). Death rates decreased for AI/AN women from 1990 to 1993 (-25.8%/year) and remained stable thereafter. Conclusions. Although rates decreased over time, AI/AN women had disproportionately higher cervical cancer incidence and mortality. The persistently higher rates among AI/AN women compared with White women require continued improvements in identifying and treating cervical cancer and precancerous lesions. (Am J Public Health. Published online ahead of print April 22, 2014: e1-e8. doi:10.2105/AJPH.2013.301681).

Wax, M. K. (2014). The role of the implantable doppler probe in free flap surgery. *The Laryngoscope, 124 Suppl 1*, S1-12.

OBJECTIVES/HYPOTHESIS: Free tissue transfer has success rates greater than 95%. Approximately 10% will require reexploration for vascular compromise. Return to the operating room within 48 hours yields the highest rate of successful salvage. Our aim was to determine whether an implantable Doppler used for intraoperative/postoperative monitoring would 1) alter the pattern of detecting flap failure and 2) alter the overall incidence of flap survival. STUDY DESIGN: Prospective analysis. METHODS: Generic and study specific data was collected. Note was made at the end of the case if revision of the vascular anastomosis was performed. Data was collected for flap outcomes in the postoperative period. RESULTS: A total of 1,236 free tissues transfers from 2001 through 2011 were analyzed. Ninety-four were outside the head and neck or the Doppler was not used/inadvertently discontinued. A total of 1,142 flaps make up the study cohort. One hundred thirty-four (11.7%) intraoperative flow problems were detected, all successfully revised. Of these, 15 (11%) required postoperative revision and five (33%) were successfully salvaged, with an overall survival 93%. A total of 1,008 flaps did not require

intraoperative revision, 62 required reexploration (6.1%), and 38 (61%) were salvaged. The overall survival was 97.6%. There were eight false positive (no intervention) and 10 false negatives. Sensitivity was 87% with specificity 99%. CONCLUSION: Intraoperative Doppler's increase the detection of immediate/incipient vascular problems. Patients requiring revision in the operating room require revision more often in the postoperative period (P = .03) and are less likely to have successful salvage and a lower flap survival rate (P = .05).

Webel, R., Hakki, M., Prichard, M. N., Rawlinson, W. D., Marschall, M., & Chou, S. (2014). Differential properties of cytomegalovirus pUL97 kinase isoforms affect viral replication and maribavir susceptibility. *Journal of Virology*, *88*(9), 4776-4785.

The human cytomegalovirus (HCMV)-encoded kinase pUL97 is required for efficient viral replication. Previous studies described two isoforms of pUL97, the full-length isoform (M1) and a smaller isoform likely resulting from translation initiation at codon 74 (M74). Here, we report the detection of a third pUL97 isoform during viral infection resulting from translation initiation at codon 157 (isoform M157). The consistent expression of isoform M157 as a minor component of pUL97 during infection with clinical and laboratory-adapted HCMV strains was suppressed when codon 157 was mutagenized. Viral mutants expressing specific isoforms were generated to compare their growth and drug susceptibility phenotypes, as well as pUL97 intracellular localization patterns and kinase activities. The exclusive expression of isoform M157 resulted in substantially reduced viral growth and resistance to the pUL97 inhibitor maribavir while retaining susceptibility to ganciclovir. Confocal imaging demonstrated reduced nuclear import of amino-terminal deletion isoforms compared to isoform M1. Isoform M157 showed reduced efficiency of various substrate protein interactions and autophosphorylation, whereas Rb phosphorylation was preserved. These results reveal differential properties of pUL97 isoforms that affect viral replication, with implications for the antiviral efficacy of maribavir. 

Weimer, M. B., & Chou, R. (2014). Research gaps on methadone harms and comparative harms: Findings from a review of the evidence for an american pain society and college on problems of drug dependence clinical practice guideline. *The Journal of Pain : Official Journal of the American*

*Pain Society*, *15*(4), 366-376.

Methadone-associated overdose deaths have dramatically increased. In order to inform an evidence-based clinical practice guideline to improve safety of methadone prescribing, the American Pain Society commissioned a systematic review on various aspects related to methadone safety. We searched Ovid MEDLINE, Cochrane Library, and PsycINFO databases through July 2012 to identify studies that addressed 1 or more of 17 Key Questions related to methadone safety; an update search was performed in 2014 for new studies related to methadone-related overdose and risks related to cardiac arrhythmias. A total of 168 studies met inclusion criteria for the review. The purpose of this article is to highlight critical research gaps in the literature related to methadone safety. These include lack of evidence on risk factors associated with methadone-overdose deaths and adverse events, limited evidence to evaluate the comparative mortality of methadone versus other opioids, insufficient evidence to fully understand the harms associated with methadone use during pregnancy, and insufficient evidence to determine effects of risk mitigation strategies such as electrocardiogram monitoring, strategies for managing patients with prolonged QTc intervals on screening, urine drug testing, alternative dosing regimens for initiation and titration of therapy, and timing of follow-up. Therefore, most guideline recommendations are based on weak evidence. More research is needed to guide safe methadone prescribing practices and decrease the adverse events associated with methadone. PERSPECTIVE: This article summarizes critical research gaps in the literature related to methadone safety, based on a systematic review commissioned by the American Pain Society. Critical research gaps were identified in a number of areas, highlighting the need for additional research to guide safer prescribing and risk mitigation strategies.

Weinstein, J. N., Akbani, R., Broom, B. M., Wang, W., Verhaak, R. G. W., McConkey, D., et al. (2014). Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*, *507*(7492), 315-322.

Urothelial carcinoma of the bladder is a common malignancy that causes approximately 150,000 deaths per year worldwide. So far, no molecularly targeted agents have been approved for treatment of the disease. As part of The Cancer Genome Atlas project, we report here an integrated analysis of 131 urothelial carcinomas to provide a comprehensive landscape of

molecular alterations. There were statistically significant recurrent mutations in 32 genes, including multiple genes involved in cell-cycle regulation, chromatin regulation, and kinase signalling pathways, as well as 9 genes not previously reported as significantly mutated in any cancer. RNA sequencing revealed four expression subtypes, two of which (papillary-like and basal/squamous-like) were also evident in microRNA sequencing and protein data. Whole-genome and RNA sequencing identified recurrent in-frame activating FGFR3-TACC3 fusions and expression or integration of several viruses (including HPV16) that are associated with gene inactivation. Our analyses identified potential therapeutic targets in 69% of the tumours, including 42% with targets in the phosphatidylinositol-3-OH kinase/AKT/mTOR pathway and 45% with targets (including ERBB2) in the RTK/MAPK pathway. Chromatin regulatory genes were more frequently mutated in urothelial carcinoma than in any other common cancer studied so far, indicating the future possibility of targeted therapy for chromatin abnormalities. 

Werner, S., Durkan, M., Jones, J., Quilici, S., & Crawford, D. (2013). Symptomatic bipartite patella: Three subtypes, three representative cases. *The Journal of Knee Surgery, 26 Suppl 1*, S72-6.
Bipartite patella can be classified into three unique subtypes; type I, II, and III. The following case series describes three representative cases of each subtype and a spectrum of location-specific treatment options for surgical care of the symptomatic bipartite patella.

Wertheimer, A. M., Bennett, M. S., Park, B., Uhrlaub, J. L., Martinez, C., Pulko, V., et al. (2014). Aging and cytomegalovirus infection differentially and jointly affect distinct circulating T cell subsets in humans. *Journal of Immunology, 192*(5), 2143-2155.
The impact of intrinsic aging upon human peripheral blood T cell subsets remains incompletely quantified and understood. This impact must be distinguished from the influence of latent persistent microorganisms, particularly CMV, which has been associated with age-related changes in the T cell pool. In a cross-sectional cohort of 152 CMV-negative individuals, aged 21-101 y, we found that aging correlated strictly to an absolute loss of naive CD8, but not CD4, T cells but, contrary to many reports, did not lead to an increase in memory T cell numbers. The loss of naive CD8 T cells was not altered by CMV in 239 subjects (range 21-96 y), but the decline in CD4+

naive cells showed significance in CMV+ individuals. These individuals also exhibited an absolute increase in the effector/effector memory CD4+ and CD8+ cells with age. That increase was seen mainly, if not exclusively, in older subjects with elevated anti-CMVAb titers, suggesting that efficacy of viral control over time may determine the magnitude of CMV impact upon T cell memory, and perhaps upon immune defense. These findings provide important new insights into the age-related changes in the peripheral blood pool of older adults, demonstrating that aging and CMV exert both distinct and joint influence upon blood T cell homeostasis in humans.

White, S. B., Tutton, S. M., Rilling, W. S., Kuhlmann, R. S., Peterson, E. L., Wigton, T. R., et al. (2014). Percutaneous in utero thoracoamniotic shunt creation for fetal thoracic abnormalities leading to nonimmune hydrops. *Journal of Vascular and Interventional Radiology : JVIR,* PURPOSE: To describe a transabdominal, transuterine Seldinger-based percutaneous approach to create a shunt for treatment of fetal thoracic abnormalities. MATERIALS AND METHODS: Five fetuses presented with nonimmune fetal hydrops secondary to fetal thoracic abnormalities causing severe mass effect. Under direct ultrasound guidance, an 18-gauge needle was used to access the malformation. Through a peel-away sheath, a customized pediatric transplant 4.5-F double J ureteral stent was advanced; the leading loop was placed in the fetal thorax, and the trailing end was left outside the fetal thorax within the amniotic cavity. RESULTS: Seven thoracoamniotic shunts were successfully placed in five fetuses; one shunt was immediately replaced because of displacement during the procedure, and another shunt was not functioning at follow-up requiring insertion of a second shunt. All fetuses had successful decompression of the thoracic malformation, allowing lung reexpansion and resolution of hydrops. Three of five mothers had meaningful (> 7 d) prolongation of their pregnancies. All pregnancies were maintained to > 30 weeks (range, 30 weeks 1 d-37 weeks 2 d). There were no maternal complications. CONCLUSIONS: A Seldinger-based percutaneous approach to draining fetal thoracic abnormalities is feasible and can allow for prolongation of pregnancy and antenatal lung development and ultimately result in fetal survival.

Wiener, R. S., Gould, M. K., Slatore, C. G., Fincke, B. G., Schwartz, L. M., & Woloshin, S. (2014). Resource use and guideline concordance in evaluation of pulmonary nodules for cancer: Too much and too little care. *JAMA Internal Medicine*,

IMPORTANCE Pulmonary nodules are common, and more will be found with implementation of lung cancer screening. How potentially malignant pulmonary nodules are evaluated may affect patient outcomes, health care costs, and effectiveness of lung cancer screening programs. Guidelines for evaluating pulmonary nodules for cancer exist, but little is known about how nodules are evaluated in the usual care setting. OBJECTIVE To characterize nodule evaluation and concordance with guidelines. DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study was conducted including detailed review of medical records from pulmonary nodule detection through evaluation completion, cancer diagnosis, or study end (December 31, 2012). The participants included 300 adults with pulmonary nodules from 15 Veterans Affairs hospitals. MAIN OUTCOMES AND MEASURES Resources used for evaluation at any Veterans Affairs facility and guideline-concordant evaluation served as the main outcomes. RESULTS Twenty-seven of 300 patients (9.0%) with pulmonary nodules ultimately received a diagnosis of lung cancer: 1 of 57 (1.8%) with a nodule of 4 mm or less, 4 of 134 (3.0%) with a nodule of 5 to 8 mm, and 22 of 109 (20.2%) with a nodule larger than 8 mm. Nodule evaluation entailed 1044 imaging studies, 147 consultations, 76 biopsies, 13 resections, and 21 hospitalizations. Radiographic surveillance (n = 277) lasted a median of 13 months but ranged from less than 0.5 months to 8.5 years. Forty-six patients underwent invasive procedures (range per patient, 1-4): 41.3% (19 patients) did not have cancer and 17.4% (8) experienced complications, including 1 death. Notably, 15 of the 300 (5.0%) received no purposeful evaluation and had no obvious reason for deferral, seemingly "falling through the cracks." Among 197 patients with a nodule detected after release of the Fleischner Society guidelines, 44.7% received care inconsistent with guidelines (17.8% overevaluation, 26.9% underevaluation). In multivariable analyses, the strongest predictor of guideline-inconsistent care was inappropriate radiologist recommendations (overevaluation relative risk, 4.6 [95% CI, 2.3-9.2]; underevaluation, 4.3 [2.7-6.8]). Other systems factors associated with underevaluation included receiving care at more than 1 facility (2.0 [1.5-2.7]) and nodule detection during an inpatient or preoperative visit (1.6 [1.1-2.5]). CONCLUSIONS AND RELEVANCE Pulmonary nodule evaluation is often inconsistent with guidelines, including

cases with no workup and others with prolonged surveillance or unneeded procedures that may cause harm. Systems to improve quality (eg, aligning radiologist recommendations with guidelines and facilitating communication across providers) are needed before lung cancer screening is widely implemented.

Williams, J. T. (2014). Desensitization of functional mu-opioid receptors increases agonist off-rate. *Molecular Pharmacology*,

Desensitization of mu-opioid receptors (MORs) develops over 5-15 min following application of some but not all opioid agonists and lasts for 10s of min following agonist removal. The decrease in function is receptor selective (homologous) and could result from (1) a reduction in receptor number or (2) a decrease in receptor coupling. The present investigation used photolysis of two caged opioid ligands in order to examine the kinetics of MOR-induced potassium conductance before and following MOR desensitization. Photolysis of a caged antagonist, caged-naloxone (CNV-NLX), blocked the current induced by a series of agonists and the time constant of decline was significantly decreased following desensitization. The increase in the rate of current decay was not observed following partial blockade of receptors with the irreversible antagonist, beta-CNA. The time constant of current decay following desensitization was never more rapid than 1s, suggesting an increased agonist off rate rather than an increase in the rate of channel closure downstream of the receptor. The rate of GIRK current activation was examined using photolysis of a caged agonist, [Leu]5enkephalin (CYLE). Following acute desensitization or partial irreversible block of MORs with beta-CNA there was an increase in the time it took to reach a peak current. The decrease in the rate of agonist-induced GIRK conductance was receptor selective and dependent on receptor number. The results indicate that opioid receptor desensitization reduced the number of functional receptors and the remaining active receptors have a reduced agonist affinity.

Williams, R. J., Masica, A. L., McBurnie, M. A., Solberg, L. I., Bailey, S. R., Hazlehurst, B., et al. (2014). Documentation of the 5 as for smoking cessation by PCPs across distinct health systems. *American Journal of Managed Care*, *20*(3), e82-e89.

Objectives: Physicians can help patients quit smoking using the 5 As of smoking cessation. This

study aimed to (1) identify the proportion of known smokers that receive smoking cessation services in the course of routine clinical practice; (2) describe demographic and comorbidity characteristics of patients receiving the 5 As in these systems; and (3) evaluate differences in performance of the 5 As across health systems, gender, and age categories. Study Design: Electronic medical records of 200 current smokers from 6 unique health systems (N = 1200) were randomly selected from 2006 to 2010. Primary care encounter progress notes were hand coded for occurrences of the 5 As. Methods: Bivariate comparisons of delivery of the 3 smoking-cessation services by site, gender, and age category were analyzed using $\chi 2$ tests. Results: About 50% of smokers were advised to quit smoking, 39% were assessed for their readiness to quit, and 54% received some type of assistance to help them quit smoking. Only 2% had a documented plan for follow-up regarding their quitting efforts (arrange). Significant differences were found among sites for documentation of receiving the 5 As and between age groups receiving assistance with quitting. There was no statistically significant difference between genders in receipt of the 5 As. Conclusions: Documentation of adherence to the 5 As varied by site and some demographics. Adjustments to protocols for addressing cessation and readiness to quit may be warranted. Health systems could apply the methodology described in this paper to assess their own performance, and then use that as a basis to guide improvement initiatives.

Winters-Stone, K. M., Lyons, K. S., Bennett, J. A., & Beer, T. M. (2014). Patterns and predictors of symptom incongruence in older couples coping with prostate cancer. *Supportive Care in Cancer*, *22*(5), 1341-1348.

Purpose: Prostate cancer survivors (PCSs) may experience persistent symptoms following treatment. If PCSs and spouses differ in their perceptions of symptoms, that incongruence may cause mismanagement of symptoms and reduced relationship quality. The purpose of this study was to examine symptom incongruence and identify the PCS and spouse characteristics associated with symptom incongruence in older couples coping with prostate cancer. Methods: Participants in the study were older PCSs (>60 years) and their spouses (N=59 couples). Symptom incongruence was determined by comparing patient and spouse independent ratings of the severity of his cancer-related symptoms. Predictor variables included PCS age, time since diagnosis, PCS comorbidity, PCS and spouse depressive symptoms, and spouse caregiving strain.

Results: PCS and spouse ratings of his symptom severity and the amount of incongruence over his symptoms varied significantly across couples. Overall, couples rated a moderate level of PCS symptom severity, but PCSs and their spouses significantly differed in their perceptions of PCS symptom severity with spouses rating severity higher (t=-2.66, df=51, p<0.01). PCS younger age and high spouse caregiver strain accounted for 29 % of incongruence in perceptions of PCS symptom severity. Conclusions: This study is among the first to show that PCSs and spouses may perceive cancer-related persistent symptoms differently. Among this older sample, younger PCS age and spouse caregiver strain were associated with incongruence in symptoms perceptions in couples. These and other factors may inform future interventions aimed at preserving relationship quality in older couples who have experienced prostate cancer. 

Woody, G., Bruce, D., Korthuis, P. T., Chhatre, S., Hillhouse, M., Jacobs, P., et al. (2014). HIV risk reduction with buprenorphine-naloxone or methadone: Findings from A randomized trial. *Journal of Acquired Immune Deficiency Syndromes (1999)*,

OBJECTIVES:: Compare HIV injecting and sex risk in patients being treated with methadone (MET) or buprenorphine-naloxone (BUP). METHODS:: Secondary analysis from a study of liver enzyme changes in patients randomized to MET or BUP who completed 24-weeks of treatment and had 4 or more blood draws. The initial 1:1 randomization was changed to 2:1 (BUP: MET) after 18 months due to higher dropout in BUP. The Risk Behavior Survey (RBS) measured past 30-day HIV risk at baseline and weeks 12 and 24. RESULTS:: Among 529 patients randomized to MET, 391 (74%) were completers; among 740 randomized to BUP, 340 (46%) were completers; 700 completed the RBS. There were significant reductions in injecting risk (p< 0.0008) with no differences between groups in mean number of times reported injecting heroin, speedball, other opiates, and number of injections; or percent who shared needles, did not clean shared needles with bleach, shared cookers, or engaged in front/back loading of syringes. The percent having multiple sex partners decreased equally in both groups (p<0.03). For males on BUP the sex risk composite increased; for males on MET, the sex risk decreased resulting in significant group differences over time (p<0.03). For females, there was a significant reduction in sex risk (p<0.02) with no group differences. CONCLUSIONS:: Among MET and BUP patients that

remained in treatment, HIV injecting risk was equally and markedly reduced, however MET retained more patients. Sex risk was equally and significantly reduced among females in both treatment conditions, but increased for males on BUP, and decreased for males on MET.

Wyatt, L. R., Finn, D. A., Khoja, S., Yardley, M. M., Asatryan, L., Alkana, R. L., et al. (2014). Contribution of P2X4 receptors to ethanol intake in male C57BL/6 mice. *Neurochemical Research*, P2X receptors (P2XRs) are a family of cation-permeable ligand-gated ion channels activated by synaptically released extracellular adenosine 5′-triphosphate. The P2X4 subtype is abundantly expressed in the central nervous system and is sensitive to low intoxicating ethanol concentrations. Genetic meta-analyses identified the p2rx4 gene as a candidate gene for innate alcohol intake and/or preference. The current study used mice lacking the p2rx4 gene (knockout, KO) and wildtype (WT) C57BL/6 controls to test the hypothesis that P2X4Rs contribute to ethanol intake. The early acquisition and early maintenance phases of ethanol intake were measured with three different drinking procedures. Further, we tested the effects of ivermectin (IVM), a drug previously shown to reduce ethanol's effects on P2X4Rs and to reduce ethanol intake and preference, for its ability to differentially alter stable ethanol intake in KO and WT mice. Depending on the procedure and the concentration of the ethanol solution, ethanol intake was transiently increased in P2X4R KO versus WT mice during the acquisition of 24-h and limited access ethanol intake. IVM significantly reduced ethanol intake in P2X4R KO and WT mice, but the degree of reduction was 50 % less in the P2X4R KO mice. Western blot analysis identified significant changes in γ-aminobutyric acidA receptor α1 subunit expression in brain regions associated with the regulation of ethanol behaviors in P2X4R KO mice. These findings add to evidence that P2X4Rs contribute to ethanol intake and indicate that there is a complex interaction between P2X4Rs, ethanol, and other neurotransmitter receptor systems. © 2014 Springer Science+Business Media New York.

Xu, T., Stephane, M., & Parhi, K. K. (2013). Classification of single-trial MEG during sentence processing for automated schizophrenia screening. *2013 6th International IEEE EMBS Conference on Neural Engineering, NER 2013,* San Diego, CA. pp. 363-366.

This paper presents a novel computer-aided system for assisting schizophrenia (SZ) diagnosis.

Power Spectral Density Ratios (PSDRs) covering 7 brain regions and 5 frequency sub-bands are extracted as features, from single-trial magnetoencephalography (MEG) recorded while subjects read sentence stimuli silently. A two-stage feature selection algorithm combining F-score and Adaptive Boosting (Adaboost) model is proposed to rank the features. The top ranked features are used to build a boosted non-linear classifier using linear decision stumps as the base classifiers. A majority voting scheme is employed to combine single trial classification results from each test subject to make final classification decisions. Following a leave-one-out cross validation procedure, the proposed system achieves 82.61% classification accuracy (92.31% specificity and 70% sensitivity) on 13 healthy controls and 10 SZ patients. The most discriminating PSDR features are selected from the right temporal, right parietal and right frontal regions and are related to alpha (8-13Hz) and beta (13-30Hz) frequency ranges. This information may help in gaining knowledge about the abnormal neural oscillations associated with sentence-level language disorder in SZ. © 2013 IEEE.

Yanamadala, V., Lin, N., Walcott, B. P., Baird, L. C., & Smith, E. R. (2014). Spontaneous regression of an epidermoid cyst of the cavernous sinus. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*,

Epidermoid cysts are rare lesions in the pediatric population. The natural history of epidermoids is usually that of slow growth, although rupture and cases of malignant transformation have been reported. Spontaneous regression of an intracranial epidermoid cyst has not previously been described to our knowledge. We present a 3-year-old boy who presented with severe vertigo. MRI was performed which revealed a 2cm non-enhancing lesion in the right cavernous sinus. The lesion was T1-hypoinsense, T2-hyperintense, and with evidence of restricted diffusion, consistent with an epidermoid cyst. The patient was followed with annual MRI studies over the next 3years, demonstrating progressive reduction in the size of the lesion over time, with complete resolution after 3years. The child's symptoms also resolved during this period. Long-term follow-up imaging at 5years showed no evident lesion. To our knowledge, this is the first report documenting spontaneous regression of an intracranial epidermoid cyst. While isolated, this finding demonstrates the potential for involution of epidermoids and lends support to the clinical practice of careful observation of these lesions, especially when located in areas associated with high

potential surgical morbidity. Importantly, the novelty of this observation suggests a need for further study to better elucidate the underlying mechanism of this regression.

Yang, P., Michaels, K. V., Courtney, R. J., Wen, Y., Greninger, D. A., Reznick, L., et al. (2014). Retinal morphology of patients with achromatopsia during early childhood: Implications for gene therapy. *JAMA Ophthalmology*,

IMPORTANCE While older children and adults with achromatopsia have been studied, less is known of young children with achromatopsia. OBJECTIVES To characterize the macular and foveal architecture of patients with achromatopsia during early childhood with handheld spectral-domain optical coherence tomographic imaging and to make phenotype-genotype correlations. DESIGN, SETTING, AND PARTICIPANTS Comparative case series of 9 patients with achromatopsia and 9 age-matched control participants at a tertiary ophthalmology referral center. MAIN OUTCOMES AND MEASURES Patients underwent complete ocular examination, full-field electroretinography, handheld spectral-domain optical coherence tomographic imaging, and screening for genetic mutations. RESULTS The mean (SD) age of the patients with achromatopsia was 4.2 (2.4) years, and the mean (SD) age of the control participants was 4.0 (2.1) years. Cone-driven responses to photopic single-flash or 30-Hz stimuli were nonrecordable in 7 patients and severely attenuated in 2. Rod-driven responses to dim scotopic single-flash stimuli were normal in 7 patients and mildly subnormal in 2. Six patients (67%) had foveal ellipsoid zone disruption, of which 1 had a hyporeflective zone. Four patients (44%) had foveal hypoplasia. The average total retinal thicknesses of the macula and fovea in the patients with achromatopsia were 14% and 17% thinner than in the control participants ($P < .001$ and $P = .001$), which was mostly due to the outer retina that was 18% and 26% thinner than in control participants (both $P < .001$), respectively. Genetic testing revealed a common homozygous mutation in CNGB3 in 5 patients with complete achromatopsia and heterozygous mutations in CNGA3 in 2 patients with incomplete achromatopsia. The youngest and worst-affected patient harbored compound heterozygous mutations in CNGB3 and a single mutation in CNGA3. CONCLUSIONS AND RELEVANCE In early childhood, there is a spectrum of foveal pathology that is milder than reported in older individuals with achromatopsia, which suggests the need for early therapeutic intervention. Neither age alone nor genotype alone predicts the degree of photoreceptor loss or

preservation. Thus, in anticipation of future gene therapy trials in humans, we propose that handheld spectral-domain optical coherence tomography is an important tool for the early assessment and stratification of macular architecture in young children with achromatopsia.

Yin, H., Xue, W., Chen, S., Bogorad, R. L., Benedetti, E., Grompe, M., et al. (2014). Genome editing with Cas9 in adult mice corrects a disease mutation and phenotype. *Nature Biotechnology*, We demonstrate CRISPR-Cas9-mediated correction of a Fah mutation in hepatocytes in a mouse model of the human disease hereditary tyrosinemia. Delivery of components of the CRISPR-Cas9 system by hydrodynamic injection resulted in initial expression of the wild-type Fah protein in approximately 1/250 liver cells. Expansion of Fah-positive hepatocytes rescued the body weight loss phenotype. Our study indicates that CRISPR-Cas9-mediated genome editing is possible in adult animals and has potential for correction of human genetic diseases.

Zebrack, B. J., Corbett, V., Embry, L., Aguilar, C., Meeske, K. A., Hayes-Lattin, B., et al. (2014). Psychological distress and unsatisfied need for psychosocial support in adolescent and young adult cancer patients during the first year following diagnosis. *Psycho-Oncology*, Purpose: Identifying at-risk adolescent and young adult (AYA) cancer patients and referring them to age-appropriate psychosocial support services may be instrumental in reducing psychological distress and promoting psychosocial adaptation. The purpose of this study is to identify trajectories of clinically significant levels of distress throughout the first year following diagnosis and to distinguish factors, including supportive care service use, that predict the extent to which AYAs report distress. Methods: In this prospective multisite study, 215 AYAs aged 15-39 years were assessed for psychological distress and psychosocial support service use within the first 4 months of diagnosis and again 6 and 12 months later. On the basis of distress scores, respondents were assigned to one of four distress trajectory groups (Resilient, Recovery, Delayed, and Chronic). Multiple logistic regression analyses examined whether demographics, clinical variables, and reports of unsatisfied need for psychosocial support were associated with distress trajectories over 1 year. Results: Twelve percent of AYAs reported clinically significant chronic distress throughout the first 12 months following diagnosis. An additional 15% reported delayed distress. Substantial proportions of AYAs reported that needs for information (57%),

counseling (41%), and practical support (39%) remained unsatisfied at 12 months following diagnosis. Not getting counseling needs met, particularly with regard to professional mental health services, was observed to be significantly associated with distress over time. Conclusions: Substantial proportions of AYAs are not utilizing psychosocial support services. Findings suggest the importance of identifying psychologically distressed AYAs and addressing their needs for mental health counseling throughout a continuum of care. © 2014 John Wiley & Sons, Ltd.

Zhang, S., Chung, W. C., Wu, G., Egan, S. E., & Xu, K. (2014). Tumor-suppressive activity of lunatic fringe in prostate through differential modulation of notch receptor activation. *Neoplasia (New York, N.Y.), 16*(2), 158-167.

Elevated Notch ligand and receptor expression has been associated with aggressive forms of prostate cancer, suggesting a role for Notch signaling in regulation of prostate tumor initiation and progression. Here, we report a critical role for Lunatic Fringe (Lfng), which encodes an O-fucosylpeptide 3-ss-N-acetylglucosaminyltransferase known to modify epidermal growth factor repeats of Notch receptor proteins, in regulation of prostate epithelial differentiation and proliferation, as well as in prostate tumor suppression. Deletion of Lfng in mice caused altered Notch activation in the prostate, associated with elevated accumulation of Notch1, Notch2, and Notch4 intracellular domains, decreased levels of the putative Notch3 intracellular fragment, as well as increased expression of Hes1, Hes5, and Hey2. Loss of Lfng resulted in expansion of the basal layer, increased proliferation of both luminal and basal cells, and ultimately, prostatic intraepithelial neoplasia. The Lfng-null prostate showed down-regulation of prostatic tumor suppressor gene NKX3.1 and increased androgen receptor expression. Interestingly, expression of LFNG and NKX3.1 were positively correlated in publically available human prostate cancer data sets. Knockdown of LFNG in DU-145 prostate cancer cells led to expansion of CD44(+)CD24(-) and CD49f(+)CD24(-) stem/progenitor-like cell population associated with enhanced prostatosphere-forming capacity. Taken together, these data revealed a tumor-suppressive role for Lfng in the prostate through differential regulation of Notch signaling.

Zhang, Z., Ashraf, M., Sahn, D. J., & Song, X. (2014). Temporally diffeomorphic cardiac motion estimation from three-dimensional echocardiography by minimization of intensity consistency

error. *Medical Physics*, *41*(5)

Purpose: Quantitative analysis of cardiac motion is important for evaluation of heart function. Three dimensional (3D) echocardiography is among the most frequently used imaging modalities for motion estimation because it is convenient, real-time, low-cost, and nonionizing. However, motion estimation from 3D echocardiographic sequences is still a challenging problem due to low image quality and image corruption by noise and artifacts. Methods: The authors have developed a temporally diffeomorphic motion estimation approach in which the velocity field instead of the displacement field was optimized. The optimal velocity field optimizes a novel similarity function, which we call the intensity consistency error, defined as multiple consecutive frames evolving to each time point. The optimization problem is solved by using the steepest descent method. Results: Experiments with simulated datasets, images of anex vivo rabbit phantom, images of in vivo open-chest pig hearts, and healthy human images were used to validate the authors' method. Simulated and real cardiac sequences tests showed that results in the authors' method are more accurate than other competing temporal diffeomorphic methods. Tests with sonomicrometry showed that the tracked crystal positions have good agreement with ground truth and the authors' method has higher accuracy than the temporal diffeomorphic free-form deformation (TDFFD) method. Validation with an open-access human cardiac dataset showed that the authors' method has smaller feature tracking errors than both TDFFD and frame-to-frame methods. Conclusions: The authors proposed a diffeomorphic motion estimation method with temporal smoothness by constraining the velocity field to have maximum local intensity consistency within multiple consecutive frames. The estimated motion using the authors' method has good temporal consistency and is more accurate than other temporally diffeomorphic motion estimation methods. 