References

Abdala, A. P., Toward, M. A., Dutschmann, M., Bissonnette, J. M., & Paton, J. F. R. (2016). Deficiency of GABAergic synaptic inhibition in the kölliker-fuse area underlies respiratory dysrhythmia in a mouse model of rett syndrome. *Journal of Physiology, 594*(1), 223-237.

Central apnoeas and respiratory irregularity are a common feature in Rett syndrome (RTT), a neurodevelopmental disorder most often caused by mutations in the methyl-CpG-binding protein 2 gene (MECP2). We used a MECP2 deficient mouse model of RTT as a strategy to obtain insights into the neurobiology of the disease and into mechanisms essential for respiratory rhythmicity during normal breathing. Previously, we showed that, systemic administration of a GABA reuptake blocker in MECP2 deficient mice markedly reduced the occurrence of central apnoeas. Further, we found that, during central apnoeas, post-inspiratory drive (adductor motor) to the upper airways was enhanced in amplitude and duration in Mecp2 heterozygous female mice. Since the pontine Kölliker-Fuse area (KF) drives post-inspiration, suppresses inspiration, and can reset the respiratory oscillator phase, we hypothesized that synaptic inhibition in this area is essential for respiratory rhythm regularity. In this study, we found that: (i) Mecp2 heterozygous mice showed deficiency of GABA perisomatic bouton-like puncta and processes in the KF nucleus; (ii) blockade of GABA reuptake in the KF of RTT mice reduced breathing irregularity; (iii) conversely, blockade of GABAA receptors in the KF of healthy rats mimicked the RTT respiratory phenotype of recurrent central apnoeas and prolonged post-inspiratory activity. Our results show that reductions in synaptic inhibition within the KF induce rhythm irregularity whereas boosting GABA transmission reduces respiratory arrhythmia in a murine model of RTT. Our data suggest that manipulation of synaptic inhibition in KF may be a clinically important strategy for alleviating the life threatening respiratory disorders in RTT. © 2016 The Physiological Society.

Abdelhamed, S., & Kurre, P. (2015). Hope and hype surrounding circulating microRNA as potential next generation AML biomarkers. *Leukemia Research,*

Abner, E. L., Nelson, P. T., Kryscio, R. J., Schmitt, F. A., Fardo, D. W., Woltjer, R. L., et al. (2016). Diabetes is associated with cerebrovascular but not alzheimer neuropathology. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association,*

INTRODUCTION: Diabetes' relationship to specific neuropathologic causes of dementia is incompletely understood. METHODS: We used logistic regression to evaluate the association between diabetes and infarcts, Braak stage, neuritic plaque score, and level of Alzheimer's neuropathologic changes in 2365 autopsied persons. In a subset of >1300 persons with available cognitive data, we examined the association between diabetes and cognition using Poisson regression. RESULTS: Diabetes increased odds of brain infarcts (odds ratio [OR] = 1.57, P < .0001), specifically lacunes (OR = 1.71, P < .0001), but not Alzheimer neuropathology. Diabetes plus infarcts was associated with lower cognitive scores at end of life than infarcts or diabetes alone, and diabetes plus high level of Alzheimer's neuropathologic changes was associated with lower mini-mental state examination scores than the pathology alone. DISCUSSION: This study supports the conclusions that diabetes increases the risk of cerebrovascular but not Alzheimer's pathology, and at least some of diabetes' relationship to cognitive impairment may be modified by neuropathology.

Abraham, A. D., Neve, K. A., & Lattal, K. M. (2016). Activation of D1/5 dopamine receptors: A common mechanism for enhancing extinction of fear and reward-seeking behaviors. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology,*

Dopamine is critical for many processes that drive learning and memory, including motivation, prediction error, incentive salience, memory consolidation, and response output. Theories of dopamine's function in these processes have, for the most part, been developed from behavioral approaches that examine learning mechanisms in appetitive tasks. A parallel and growing literature indicates that dopamine signaling is involved in consolidation of memories into stable representations in aversive tasks such as fear conditioning. Relatively little is known about how dopamine may modulate memories that form during extinction, when organisms learn that the relation between previously associated events is severed. We investigated whether fear and reward extinction share common mechanisms that could be enhanced with dopamine D1/5 receptor activation. Pharmacological activation of dopamine D1/5 receptors (with SKF 81297) enhanced extinction of both cued and contextual fear. These effects also occurred in the extinction of cocaine-induced conditioned place preference, suggesting that the observed effects

on extinction were not specific to a particular type of procedure (aversive or appetitive). A cAMP/PKA biased D1 agonist (SKF 83959) did not affect fear extinction, whereas a broadly efficacious D1 agonist (SKF 83822) promoted fear extinction. Together, these findings show that dopamine D1/5 receptor activation is a target for the enhancement of fear or reward extinction.Neuropsychopharmacology accepted article preview online, 14 January 2016. doi:10.1038/npp.2016.5.

Abuzinadah, A. R., Alanazy, M. H., Almekhlafi, M. A., Duan, Y., Zhu, H., Mazighi, M., et al. (2016). Stroke recurrence rates among patients with symptomatic intracranial vertebrobasilar stenoses: Systematic review and meta-analysis. *Journal of NeuroInterventional Surgery, 8*(2), 112-116. Background A recent randomized trial of patients with primarily anterior circulation intracranial artery stenosis showed that intensive medical therapy was superior to intracranial stenting in preventing recurrent stroke. The rate of stroke recurrence or death in symptomatic intracranial vertebrobasilar stenosis with medical therapy alone may be especially high, and rates compared with endovascular therapy need further study. Methods We conducted a systematic review and metaanalysis of studies reporting the rates of stroke recurrence or death (the primary outcome) in symptomatic intracranial vertebrobasilar stenosis with medical or endovascular treatment over a minimum follow-up period of 6 months. We included all studies in any language indexed in MEDLINE or EMBASE, supplemented by bibliography searches and by contacting the authors. The secondary endpoints were stroke recurrence, and basilar artery and vertebral artery stroke recurrence rates. Results 23 studies (592 medical treatment patients and 480 endovascular treatment patients) were included. The risk of combined stroke recurrence or death was 14.8 per 100 person-years (95% CI 9.5 to 20.1) in the medical group compared with 8.9 per 100 person-years (95% CI 6.9 to 11.0) in the endovascular group. The incidence rate ratio was 1.3 (95% CI 1.0 to 1.7). The stroke recurrence rate was 9.6 per 100 person-years (95% CI 5.1 to 14.1) in the medical group compared with 7.2 per 100 personyears (95% CI 5.5 to 9.0) in the endovascular group. Conclusions Our results showed that the risk of stroke recurrence or death or the risk of stroke recurrence alone was comparable between the medical and endovascular therapy groups. A small preventive effect of endovascular therapy may exist, particularly if the 30 day postprocedural risk is reduced.

Ahamad, K., Korthuis, P. T., Lum, P. J., Johnson, C., & Wood, E. (2016). A delayed injection-site reaction in a patient receiving extended release naltrexone. *Substance Abuse,* , 0.

BACKGROUND: Pharmacotherapy, such as oral naltrexone, has proven effective in treating alcohol use disorder, though medication adherence has presented challenges. While a formulation of extended-release naltrexone for intramuscular injection has been developed to counter daily adherence issues, injection-site reactions can occur within days of depot injection. CASE: We report a case of an individual with alcohol use disorder who had a previously undescribed delayed injection-site reaction that occurred 11 days after injection. Subsequent challenge with the medication resulted in recurrence of the reaction. DISCUSSION: While extended-release naltrexone is generally well tolerated, injection site reactions can complicate treatment and can appear more than 10 days after medication administration.

Ahluwalia, S. C., Schreibeis-Baum, H., Prendergast, T. J., Reinke, L. F., & Lorenz, K. A. (2016). Nurses as intermediaries: How critical care nurses perceive their role in family meetings. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses, 25*(1), 33-38.

BACKGROUND: Nurses' involvement in family meetings in the intensive care unit is central to supporting consistent communication and shared understanding within the care team and with patients and patients' family members. Evidence suggests the existence of major barriers to the effective participation and contribution of nurses during family meetings. OBJECTIVES: To characterize the nature and extent of nurses' involvement in family meetings in the intensive care unit, including identifying barriers to nurses' participation and opportunities for involvement. METHODS: Meetings with focus groups of nurses at a Veterans Affairs medical intensive care unit were recorded, transcribed, and qualitatively analyzed by using the constant comparative method. RESULTS: Thirty critical care nurses participated in 6 focus groups. Three major themes describing nurses' involvement in family meetings were identified: nurses can play multiple roles in supporting conduct in family meetings, nurses face critical barriers to fully realizing these roles, and nurses end up as intermediaries in family meetings. Subthemes pertained to being well positioned to act as the patient's advocate, yet feeling undervalued and underempowered to contribute important information in family meetings, often resulting in mixed messages about

care preferences, prognosis, or goals of care that nurses did not feel able to address during the meeting. CONCLUSION: Nurses are positioned to play essential roles in family meetings, but their full involvement remains unrealized. Communication training and greater attention to nurses' empowerment and to facilitating the nurse-physician relationship in the context of family meetings most likely would increase appropriate involvement of nurses in the meetings.

Ahmed, A., Maroulakos, G., & Garaicoa, J. (2016). Acrylic resin guide for locating the abutment screw access channel of cement-retained implant prostheses. *The Journal of Prosthetic Dentistry,* Abutment screw loosening represents a common and challenging technical complication of cement-retained implant prostheses. This article describes the fabrication of a simple and accurate poly(methyl methacrylate) guide for identifying the location and angulation of the abutment screw access channel of a cement-retained implant prosthesis with a loosened abutment screw.

Ahn, J., Lee, H. M., Lim, J. K., Pan, C. Q., Nguyen, M. H., Ray Kim, W., et al. (2016). Entecavir safety and effectiveness in a national cohort of treatment-naïve chronic hepatitis B patients in the US - the ENUMERATE study. *Alimentary Pharmacology and Therapeutics, 43*(1), 134-144. Background Entecavir (ETV) has been shown to be safe and efficacious in randomised controlled trials in highly selected patients with hepatitis B virus (HBV) infection. Aim To determine the safety and effectiveness of ETV in 'real-world' HBV patients in the United States (US). Methods Treatment-naïve HBV patients ≥18 years old who received ETV for ≥12 months between 2005 and 2013 were included in a retrospective, cohort study. Rates of ALT normalisation, undetectable HBV DNA, HBeAg and HBsAg loss/seroconversion, adverse events (AE) and clinical outcomes were evaluated. Results Of 841 patients, 658 [65% male, 83% Asian; median age 47 years] met the inclusion criteria. 36% were HBeAg+ and 9.3% cirrhotic. 89% had abnormal ALT. Baseline median HBV DNA was 5.8 log 10 IU/mL. Median duration of ETV treatment was 4 years. Rates of ALT normalisation at 1, 3 and 5 years were 37.2%, 48.7% and 56.2% in HBeAg+ and 39.6%, 46.8% and 55.6% in HBeAg- patients. HBV DNA was undetectable at 1, 3 and 5 years in 34.6%, 64.7% and 84.6% in HBeAg+ patients, and 81.9%, 90.3% and 96.2% in HBeAg patients. Five-year cumulative probability of HBeAg loss and seroconversion was 46% and 33.7% and

HBsAg loss was 4.6%. ETV was discontinued due to adverse events in 1.2% of patients. Hepatic decompensation occurred in 0.8%, liver cancer in 2.7% and death in 0.6%. Conclusion Entecavir treatment was safe in a large cohort of US patients, but ALT normalisation and hepatitis B virus DNA suppression rates were lower than previously reported in clinical trials. © 2015 John Wiley & Sons Ltd.

Ahuja, S., Mukund, S., Deng, L., Khakh, K., Chang, E., Ho, H., et al. (2015). Structural basis of Nav1.7 inhibition by an isoform-selective small-molecule antagonist. *Science, 350*(6267) Voltage-gated sodium (Nav) channels propagate action potentials in excitable cells. Accordingly, Nav channels are therapeutic targets for many cardiovascular and neurological disorders. Selective inhibitors have been challenging to design because the nine mammalian Nav channel isoforms share high sequence identity and remain recalcitrant to high-resolution structural studies.Targeting the human Nav1.7 channel involved in pain perception,we present a protein-engineering strategy that has allowed us to determine crystal structures of a novel receptor site in complex with isoform-selective antagonists. GX-936 and related inhibitors bind to the activated state of voltage-sensor domain IV (VSD4),where their anionic aryl sulfonamide warhead engages the fourth arginine gating charge on the S4 helix. By opposing VSD4 deactivation, these compounds inhibit Nav1.7 through a voltage-sensor trapping mechanism, likely by stabilizing inactivated states of the channel. Residues from the S2 and S3 helices are key determinants of isoform selectivity, and bound phospholipids implicate themembrane as a modulator of channel function and pharmacology. Our results help to elucidate the molecular basis of voltage sensing and establish structural blueprints to design selective Nav channel antagonists.

Akinseye, O. A., Ojike, N. I., Akinseye, L. I., Dhandapany, P. S., & Pandi-Perumal, S. R. (2015). Association of sleep duration with stroke in diabetic patients: Analysis of the national health interview survey. *Journal of Stroke and Cerebrovascular Diseases : The Official Journal of National Stroke Association,*

BACKGROUND: Habitual sleep duration is increasingly being recognized as an important risk factor for stroke. We sought to describe the association between sleep duration and stroke in a cohort of individuals with diabetes. METHODS: Data from the National Health Interview Survey

for the years 2004-2013 were used. Only those answering "yes" to the question "Have you EVER been told by a doctor or other health professional that you have diabetes or sugar diabetes?" were included in the analysis. Sleep duration was categorized as short (/=9 hours). Self-reported diagnosis of stroke was the main outcome of interest. FINDINGS: A total number of 26,364 self-reported diabetic individuals provided data for analysis. Stroke was reported in 9.1% of short sleepers, 16.1% of long sleepers, and 8.3% of normative sleepers (P < .05). In the unadjusted model, short and long sleepers had an increased odds of stroke compared to normal sleepers (odds ratio [OR] = 1.12, 95% confidence interval [CI]: 1.02-1.23, P = .01; and OR = 2.18, 95% CI: 1.96-2.42, P = .01; respectively), but the association between short sleep and stroke became nonsignificant after multivariate adjustment (OR = 1.15, 95% CI: .95-1.40, P = .16) except in white participants. The association between long sleep duration and stroke persisted (OR = 1.46, 95% CI: 1.16-1.84, P = .01), especially in males (OR = 1.62, 95% CI: 1.14-2.28) and in white participants (OR = 1.97, 95% CI: 1.47-2.65). CONCLUSION: In diabetic patients, abnormal sleep duration was associated with increased risk of stroke, and this association varied among different sex and ethnic groups.

Alarcón, G., Ray, S., & Nagel, B. J. (2015). Lower working memory performance in overweight and obese adolescents is mediated by white matter microstructure. *Journal of the International Neuropsychological Society,* , 1-12.

Objectives: Elevated body mass index (BMI) is associated with deficits in working memory, reduced gray matter volume in frontal and parietal lobes, as well as changes in white matter (WM) microstructure. The current study examined whether BMI was related to working memory performance and blood oxygen level dependent (BOLD) activity, as well as WM microstructure during adolescence. Methods: Linear regressions with BMI and (1) verbal working memory BOLD signal, (2) spatial working memory BOLD signal, and (3) fractional anisotropy (FA), a measure of WM microstructure, were conducted in a sample of 152 healthy adolescents ranging in BMI. Results: BMI was inversely related to IQ and verbal and spatial working memory accuracy; however, there was no significant relationship between BMI and BOLD response for either verbal or spatial working memory. Furthermore, BMI was negatively correlated with FA in the left superior longitudinal fasciculus (SLF) and left inferior longitudinal fasciculus (ILF). ILF FA and IQ

significantly mediated the relationship between BMI and verbal working memory performance, whereas SLF FA, but not IQ, significantly mediated the relationship between BMI and accuracy of both verbal and spatial working memory. Conclusions: These findings indicate that higher BMI is associated with decreased FA in WM fibers connecting brain regions that support working memory, and that WM microstructural deficits may underlie inferior working memory performance in youth with higher BMI. Of interest, BMI did not show the same relationship with working memory BOLD activity, which may indicate that changes in brain structure precede changes in function. (JINS, 2015, 21, 1–12) Copyright © The International Neuropsychological Society 2015

Allen, A. R., Raber, J., Chakraborti, A., Sharma, S., & Fike, J. R. (2015). 56Fe irradiation alters spine density and dendritic complexity in the mouse hippocampus. *Radiation Research, 184*(6), 586-594.

A unique feature of the space radiation environment is the presence of high-energy charged particles, which can be significantly hazardous to space flight crews who are exposed during a mission. Health risks associated with high-LET radiation exposure include cognitive injury. The pathogenesis of this injury is unknown but may involve modifications to dendritic structure and/or alterations in dendritic spine density and morphology. In this study, 24 two-month-old C57BL6/J male mice were either whole-body irradiated with 0.5 Gy 56Fe (600 MeV/n; n = 12) or sham irradiated (n = 12). Three months postirradiation animals were tested for locomotor activity and habituation. After behavioral testing, animals were euthanized and the brains were flash frozen. Compared to sham-irradiated mice, irradiated mice moved less when first introduced to the environment, although they did recognize the environment when re-exposed to it one day later. Exposure to 56Fe radiation significantly compromised the dendritic architecture and reduced spine density throughout the hippocampal tri-synaptic network. To our knowledge, these data represents the first reported evidence that high-LET radiation has deleterious effects on mature neurons associated with hippocampal learning and memory. © 2015 by Radiation Research Society.

Allott, E. H., Howard, L. E., Aronson, W. J., Terris, M. K., Kane, C. J., Amling, C. L., et al. (2016). Racial differences in the association between preoperative serum cholesterol and prostate cancer recurrence: Results from the SEARCH database. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology,*

BACKGROUND: Black men are disproportionately affected by both cardiovascular disease and prostate cancer. Epidemiologic evidence linking dyslipidemia, an established cardiovascular risk factor, and prostate cancer progression is mixed. As existing studies were conducted in predominantly non-black populations, research in black men is lacking. METHODS: We identified 628 black and 1,020 non-black men who underwent radical prostatectomy and never used statins before surgery in the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Median follow up was 2.9 years. The impact of preoperative hypercholesterolemia on risk of biochemical recurrence was examined using multivariable, race-stratified proportional hazards. In secondary analysis, we examined associations with low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides, overall and among men with dyslipidemia. RESULTS: High cholesterol was associated with increased risk of recurrence in black (HRper10mg/dl 1.06; 95%CI 1.02-1.11) but not non-black men (HRper10mg/dl 0.99; 95%CI 0.95-1.03; p-interaction=0.011). Elevated triglycerides were associated with increased risk in both black and non-black men (HRper10mg/dl 1.02; 95%CI 1.00-1.03 and 1.02; 95%CI 1.00-1.02, respectively; p-interaction=0.458). There were no significant associations between LDL or HDL and recurrence risk in either race. Associations with cholesterol, LDL and triglycerides were similar among men with dyslipidemia, but low HDL was associated with increased risk of recurrence in black, but not non-black men with dyslipidemia (p-interaction=0.047). CONCLUSIONS: Elevated cholesterol was a risk factor for recurrence in black but not non-black men, whereas high triglycerides were associated with increased risk regardless of race. IMPACT: Significantly contrasting associations by race may provide insight into prostate cancer racial disparities.

Alonso, E., Aramendi, E., Daya, M., Irusta, U., Chicote, B., Russell, J. K., et al. (2016). Circulation detection using the electrocardiogram and the thoracic impedance acquired by defibrillation pads. *Resuscitation, 99*, 56-62.

Aim: To develop and evaluate a method to detect circulation in the presence of organized rhythms (ORs) during resuscitation using signals acquired by defibrillation pads. Methods: Segments containing electrocardiogram (ECG) and thoracic impedance (TI) signals free of artifacts were used. The ECG corresponded to ORs classified as pulseless electrical activity (PEA) or pulse-generating rhythm (PR). A first dataset containing 1091 segments was split into training and test sets to develop and validate the circulation detector. The method processed ECG and TI to obtain the impedance circulation component (ICC). Morphological features were extracted from ECG and ICC, and combined into a classifier to discriminate between PEA and PR. The performance of the method was evaluated in terms of sensitivity (PR) and specificity (PEA). A second dataset (86 segments from different patients) was used to assess two application of the method: confirmation of arrest by recognizing absence of circulation during ORs and detection of return of spontaneous circulation (ROSC) during resuscitation. In both cases, time to confirmation of arrest/ROSC was determined. Results: The method showed a sensitivity/specificity of 92.1%/90.3% and 92.2%/91.9% for training and test sets respectively. The method confirmed cardiac arrest with a specificity of 93.3% with a median delay of 0 s after the first OR annotation. ROSC was detected with a sensitivity of 94.4% with a median delay of 57. s from ROSC onset. Conclusion: The method showed good performance, and can be reliably used to distinguish perfusing from non-perfusing ORs.

Amaral, A. F., Coton, S., Kato, B., Tan, W. C., Studnicka, M., Janson, C., et al. (2016). Lung function defects in treated pulmonary tuberculosis patients. *The European Respiratory Journal, 47*(1), 352-353.

Amrock, S. M., & Weitzman, M. (2016). Multiple biomarkers for mortality prediction in peripheral arterial disease. *Vascular Medicine (London, England),*

Few studies have assessed which biomarkers influence mortality risk among those with peripheral arterial disease (PAD). We analyzed data from 556 individuals identified to have PAD (i.e. ankle-brachial index 0.9) with available measurements of C-reactive protein, the neutrophil-to-lymphocyte ratio (NLR), homocysteine, and the urinary albumin-to-creatinine ratio (UACR) in the 1999-2004 National Health and Nutrition Examination Survey. We investigated whether a

combination of these biomarkers improved the prediction of all-cause and cardiovascular mortality beyond conventional risk factors. During follow-up (median, 8.1 years), 277 of 556 participants died; 63 deaths were attributed to cardiovascular disease. After adjusting for conventional risk factors, Cox proportional-hazards models showed the following to be most strongly associated with all-cause mortality (each is followed by the adjusted hazard ratio [HR] per 1 standard deviation increment in the log values): homocysteine (1.31), UACR (1.21), and NLR (1.20). UACR alone significantly predicted cardiovascular mortality (1.53). Persons in the highest quintile of multimarker scores derived from regression coefficients of significant biomarkers had elevated risks of all-cause mortality (adjusted HR, 2.45; 95% CI, 1.66-3.62; p for trend, <0.001) and cardiovascular mortality (adjusted HR, 2.20; 95% CI, 1.02-4.71; p for trend, 0.053) compared to those in the lowest two quintiles. The addition of continuous multimarker scores to conventional risk factors improved risk stratification of all-cause mortality (integrated discrimination improvement [IDI], 0.162; p<0.00001) and cardiovascular mortality (IDI, 0.058; p<0.00001). In conclusion, the addition of a continuous multimarker score to conventional risk factors improved mortality prediction among patients with PAD.

Andraweera, P. H., Bobek, G., Bowen, C., Burton, G. J., Correa Frigerio, P., Chaparro, A., et al. (2015). IFPA meeting 2015 workshop report: Mechanistic role of the placenta in fetal programming; biomarkers of placental function and complications of pregnancy; late onset fetal growth restriction surveillance and monitoring. *Placenta,*

Workshops are an integral component of the annual International Federation of Placenta Association (IFPA) meeting, allowing for networking and focused discussion related to specialized topics on the placenta. At the 2015 IFPA meeting (Brisbane, Australia) twelve themed workshops were held, three of which are summarized in this report. These workshops focused on various aspects of placental function, particularly in cases of placenta-mediated disease. Collectively, these inter-connected workshops highlighted the role of the placenta in fetal programming, the use of various biomarkers to monitor placental function across pregnancy, and the clinical impact of novel diagnostic and surveillance modalities in instances of late onset fetal growth restriction (FGR).

Andrea, S. B., Siegel, S. A., & Teo, A. R. (2015). TEMPORARY REMOVAL: Social support and health service use in depressed adults: Findings from the national health and nutrition examination survey. *General Hospital Psychiatry,*

Andrea, S. B., Siegel, S. A. R., & Teo, A. R. (2015). Social support and health service use in depressed adults: Findings from the national health and nutrition examination survey. *General Hospital Psychiatry,*

Objective: We investigated the relationship between social support and health service use among men and women with depression. Methods: Participants were 1379 adults with symptoms of depression (Patient Health Questionnaire-9 score ≥. 5) in the National Health and Nutrition Examination Survey. Using the framework of the Andersen Behavioral Model of Health Services Use, multivariable regression models used social support, stratified by depression severity, to estimate association with utilization of mental health and nonmental health services. Partial F-tests examined a priori interactions between social support and gender. Results: Among those with adequate social support, odds of seeing a nonmental health provider were much higher when depression was moderate [Odds Ratio (OR): 2.6 (1.3-5.3)] or severe [OR: 3.2 (1.2-8.7)], compared to those lacking social support. Conversely, odds of mental health service use were 60% lower among those with moderate depression [OR: 0.4 (0.2-1.0)] when social support was adequate as opposed to inadequate. Social support was unrelated to service use when depression was mild. Gender moderated the relationship between social support and health service use among individuals with severe depression. Conclusions: Social support has opposite associations with mental and nonmental health service use among adults with clinically significant depression. This association is largely attributable to the effect of male gender on the relationship between social support and health service use. © 2015.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, eugenol, CAS registry number 97-53-0. *Food and Chemical Toxicology,*

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity,

reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Reproductive toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 230 mg/kg/day. A gavage multigenerational continuous breeding study conducted in rats on a suitable read across analog resulted in a MOE of 12,105 while considering 22.6% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable. © 2015 Elsevier Ltd.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, isoeugenol, CAS registry number 97-54-1. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 37.5 mg/kg/day. A gavage 13-week subchronic toxicity study conducted in mice resulted in a MOE of 5769 while considering 38.4% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, l-linalool, CAS registry number 126-91-0. *Food and Chemical Toxicology,*

The use of this material under current use conditions is supported by the existing information.This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined using a suitable read across analog to have the most conservative systemic exposure derived NO[A]EL of 36 mg/kg/day. A dermal 90-day subchronic toxicity study conducted in rats resulted in a MOE of 2250 while considering 14.4% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable. © 2015 Elsevier Ltd.

Armstrong, A. J., Halabi, S., Eisen, T., Broderick, S., Stadler, W. M., Jones, R. J., et al. (2016). Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): A multicentre, open-label, randomised phase 2 trial. *The Lancet.Oncology,* BACKGROUND: Non-clear cell renal cell carcinomas are histologically and genetically diverse kidney cancers with variable prognoses, and their optimum initial treatment is unknown. We aimed to compare the mTOR inhibitor everolimus and the VEGF receptor inhibitor sunitinib in patients with non-clear cell renal cell carcinoma. METHODS: We enrolled patients with metastatic papillary, chromophobe, or unclassified non-clear cell renal cell carcinoma with no history of previous systemic treatment. Patients were randomly assigned (1:1) to receive everolimus (10 mg/day) or sunitinib (50 mg/day; 6-week cycles of 4 weeks with treatment followed by 2 weeks without treatment) administered orally until disease progression or unacceptable toxicity. Randomisation was stratified by Memorial Sloan Kettering Cancer Center risk group and papillary histology. The primary endpoint was progression-free survival in the intention-to-treat population using the RECIST 1.1 criteria. Safety was assessed in all patients who were randomly assigned to treatment. This study is registered with ClinicalTrials.gov, number NCT01108445. FINDINGS: Between Sept 23, 2010, and Oct 28, 2013, 108 patients were randomly assigned to receive either sunitinib (n=51) or everolimus (n=57). As of December, 2014, 87 progression-free survival events had occurred with two remaining active patients, and the trial was closed for the primary analysis. Sunitinib significantly increased progression-free survival compared with everolimus (8.3 months [80% CI 5.8-11.4] vs 5.6 months [5.5-6.0]; hazard ratio 1.41 [80% CI 1.03-1.92]; p=0.16), although heterogeneity of the treatment effect was noted on the basis of histological subtypes and prognostic risk groups. No unexpected toxic effects were reported, and the most common grade 3-4 adverse events were hypertension (12 [24%] of 51 patients in the sunitinib group vs one [2%] of 57 patients in the everolimus group), infection (six [12%] vs four [7%]), diarrhoea (five [10%] vs one [2%]), pneumonitis (none vs five [9%]), stomatitis (none vs five [9%]), and hand-foot syndrome (four [8%] vs none). INTERPRETATION: In patients with metastatic non-clear cell renal cell carcinoma, sunitinib improved progression-free survival compared with everolimus. Future trials of novel agents should account for heterogeneity in disease outcomes based on genetic, histological, and prognostic factors. FUNDING: Novartis and Pfizer.

Bacchi, A., Nelson, M., & Pfeifer, C. S. (2015). Characterization of methacrylate-based composites containing thio-urethane oligomers. *Dental Materials,*

Objective: To evaluate the ability of thio-urethane oligomers to improve the properties of restorative composite resins. Methods: Oligomers were synthesized by combining 1,6-hexanediol-diissocyante (aliphatic) with pentaerythritol tetra-3-mercaptopropionate (PETMP) or 1,3-bis(1-isocyanato-1-methylethyl)benzene (aromatic) with trimethylol-tris-3-mercaptopropionate (TMP), at 1:2 isocyanate:thiol, leaving pendant thiols. Oligomers were added at 0-20wt% to BisGMA-TEGDMA (70-30wt%). Silanated inorganic fillers were added (70wt%). Materials were photoactivated at 800mW/cm2 filtered to 320-500nm. Near-IR was used to follow degree of methacrylate conversion (DC). Mechanical properties were evaluated in three-point bending with 2mm×2mm×25mm bars for flexural strength/modulus and toughness (FS/E, and T) according to ISO 4049, and 2mm×5mm×25mm notched specimens for fracture toughness (K IC). Polymerization stress (PS) was measured on the Bioman. Results were analyzed with ANOVA/Tukey's test (α =5%). Results: Significant increase in DC was observed in thio-urethane-containing materials especially for the group with 20wt% of aliphatic version. Materials composed by oligomers also promoted higher FS, E, and K IC in comparison to controls irrespective of thio-urethane type. A significant increase in toughness was detected by ANOVA, but not distinguished in the groups. The PS was significantly reduced by the presence of thio-urethane for almost all groups. Conclusions: The use of thio-urethane oligomer to compose methacrylate-based restorative composite promote increase in DC, FS, E and K IC while significant reduces PS. Significance: A simple additive was shown to reduce stress while increasing convrersion and mechanical properties, mainly fracture toughness. This has he potential of increasing the service life of dental composites, without changing current operatory procedures. © 2015 Academy of Dental Materials.

Bacchi, A., Nelson, M., & Pfeifer, C. S. (2016). Characterization of methacrylate-based composites containing thio-urethane oligomers. *Dental Materials : Official Publication of the Academy of Dental Materials,*

OBJECTIVE: To evaluate the ability of thio-urethane oligomers to improve the properties of restorative composite resins. METHODS: Oligomers were synthesized by combining 1,6-

hexanediol-diissocyante (aliphatic) with pentaerythritol tetra-3-mercaptopropionate (PETMP) or 1,3-bis(1-isocyanato-1-methylethyl)benzene (aromatic) with trimethylol-tris-3-mercaptopropionate (TMP), at 1:2 isocyanate:thiol, leaving pendant thiols. Oligomers were added at 0-20wt% to BisGMA-TEGDMA (70-30wt%). Silanated inorganic fillers were added (70wt%). Materials were photoactivated at 800mW/cm2 filtered to 320-500nm. Near-IR was used to follow degree of methacrylate conversion (DC). Mechanical properties were evaluated in three-point bending with 2mmx2mmx25mm bars for flexural strength/modulus and toughness (FS/E, and T) according to ISO 4049, and 2mmx5mmx25mm notched specimens for fracture toughness (KIC). Polymerization stress (PS) was measured on the Bioman. Results were analyzed with ANOVA/Tukey's test (alpha=5%). RESULTS: Significant increase in DC was observed in thio-urethane-containing materials especially for the group with 20wt% of aliphatic version. Materials composed by oligomers also promoted higher FS, E, and KIC in comparison to controls irrespective of thio-urethane type. A significant increase in toughness was detected by ANOVA, but not distinguished in the groups. The PS was significantly reduced by the presence of thio-urethane for almost all groups. CONCLUSIONS: The use of thio-urethane oligomer to compose methacrylate-based restorative composite promote increase in DC, FS, E and KIC while significant reduces PS. SIGNIFICANCE: A simple additive was shown to reduce stress while increasing convrersion and mechanical properties, mainly fracture toughness. This has he potential of increasing the service life of dental composites, without changing current operatory procedures.

Baeten, D., Sieper, J., Braun, J., Baraliakos, X., Dougados, M., Emery, P., et al. (2015). Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. *New England Journal of Medicine, 373*(26), 2534-2548.

Background: Secukinumab is an anti-interleukin-17A monoclonal antibody that has been shown to control the symptoms of ankylosing spondylitis in a phase 2 trial. We conducted two phase 3 trials of secukinumab in patients with active ankylosing spondylitis. Methods: In two double-blind trials, we randomly assigned patients to receive secukinumab or placebo. In MEASURE 1, a total of 371 patients received intravenous secukinumab (10 mg per kilogram of body weight) or matched placebo at weeks 0, 2, and 4, followed by subcutaneous secukinumab (150 mg or 75

mg) or matched placebo every 4 weeks starting at week 8. In MEASURE 2, a total of 219 patients received subcutaneous secukinumab (150 mg or 75 mg) or matched placebo at baseline; at weeks 1, 2, and 3; and every 4 weeks starting at week 4. At week 16, patients in the placebo group were randomly reassigned to subcutaneous secukinumab at a dose of 150 mg or 75 mg. The primary end point was the proportion of patients with at least 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) response criteria at week 16. Results: In MEASURE 1, the ASAS20 response rates at week 16 were 61%, 60%, and 29% for subcutaneous secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($P<0.001$ for both comparisons with placebo); in MEASURE 2, the rates were 61%, 41%, and 28% for subcutaneous secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($P<0.001$ for the 150-mg dose and $P = 0.10$ for the 75-mg dose). The significant improvements were sustained through 52 weeks. Infections, including candidiasis, were more common with secukinumab than with placebo during the placebo-controlled period of MEASURE 1. During the entire treatment period, pooled exposure-adjusted incidence rates of grade 3 or 4 neutropenia, candida infections, and Crohn's disease were 0.7, 0.9, and 0.7 cases per 100 patientyears, respectively, in secukinumab-treated patients. Conclusions: Secukinumab at a subcutaneous dose of 150 mg, with either subcutaneous or intravenous loading, provided significant reductions in the signs and symptoms of ankylosing spondylitis at week 16. Secukinumab at a subcutaneous dose of 75 mg resulted in significant improvement only with a higher intravenous loading dose.

Baker-Groberg, S. M., Lattimore, S., Recht, M., McCarty, O. J., & Haley, K. M. (2016). Assessment of neonatal platelet adhesion, activation, and aggregation. *Journal of Thrombosis and Haemostasis : JTH,*

BACKGROUND: Acquired and inherited bleeding disorders may present in the neonatal period with devastating lifelong effects. Diagnosing bleeding disorders in the neonatal population could aid in preventing and treating the associated complications. However, currently available platelet function testing is limited in neonates owing to difficulties obtaining adequate blood volume, lack of normal reference ranges, and an incomplete understanding of the neonatal platelet functional phenotype. OBJECTIVE: Develop small-volume, whole blood platelet function assays to quantify

and compare neonatal and adult platelet function. METHODS AND RESULTS: Peripheral blood was obtained from healthy, full-term neonates at 24-hours of life. Platelet activation, secretion, and aggregation were measured via flow cytometry. Platelet adhesion and aggregation were assessed under static and flow conditions. As compared to adult platelets, peripheral neonatal platelet P-selectin expression and integrin glycoprotein (GP) IIbIIIa activation was significantly reduced in response to the G protein-coupled receptor (GPCR)-agonists thrombin receptor activator peptide-6 (TRAP-6), adenosine 5'-diphosphate (ADP), and U46619 and the immunoreceptor tyrosine-based activation motif (ITAM)-signaling pathway agonists collagen-related peptide (CRP) and rhodocytin. Neonatal platelet aggregation was markedly reduced in response to TRAP-6, ADP, U46619, CRP, and rhodocytin compared to adult platelets. The extent of neonatal and adult platelet adhesion and aggregate formation under static and shear conditions on collagen and von Willebrand factor (VWF) were similar. CONCLUSIONS: As compared to adult platelets, we found neonatal platelet activation and secretion were blunted in response to GPCR- or ITAM-agonists, while the extent of neonatal platelet adhesion and aggregate formation was similar to adult platelets.

Balaji, S., Kron, J., & Stecker, E. C. (2016). Catheter ablation of recurrent lone atrial fibrillation in teenagers with a structurally normal heart. *Pacing and Clinical Electrophysiology : PACE, 39*(1), 60-64.

BACKGROUND: Atrial fibrillation (AF) is rare in teenagers. There are few reports and no clear guidelines on the management of AF with catheter ablation in teenagers. METHODS: A case series of teenagers (<18 years) with paroxysmal AF and a structurally normal heart who underwent catheter ablation was undertaken. RESULTS: Four teenage boys aged 15-17 years underwent catheter ablation of AF. All but one had failed antiarrhythmic medical therapy. Two had focal triggers and underwent culprit vein isolation (one recurred and so underwent isolation of an additional vein), and two had no focal triggers identified and so underwent isolation of all four pulmonary veins (PVs). At follow-up ranging from 2-6 years, one patient who underwent isolation of all four veins had recurrence of paroxysmal AF. All others have had medium and long-term success with complete absence of AF. None are on long-term antiarrhythmic therapy. No patient had a procedural or postprocedure complication. CONCLUSIONS: A cautious attempt at

catheter ablation may be appropriate in teenagers with paroxysmal AF and a structurally normal heart who fail pharmacologic therapy. Culprit vein(s) isolation should be preferred if possible but if no focal triggers are identified, isolation of all PVs appears to be beneficial.

Bandrowski, A., Brush, M., Grethe, J. S., Haendel, M. A., Kennedy, D. N., Hill, S., et al. (2015). The resource identification initiative: A cultural shift in publishing. *Brain and Behavior,*

A central tenet in support of research reproducibility is the ability to uniquely identify research resources, that is, reagents, tools, and materials that are used to perform experiments. However, current reporting practices for research resources are insufficient to identify the exact resources that are reported or to answer basic questions such as "How did other studies use resource X?" To address this issue, the Resource Identification Initiative was launched as a pilot project to improve the reporting standards for research resources in the methods sections of papers and thereby improve identifiability and scientific reproducibility. The pilot engaged over 25 biomedical journal editors from most major publishers, as well as scientists and funding officials. Authors were asked to include Research Resource Identifiers (RRIDs) in their manuscripts prior to publication for three resource types: antibodies, model organisms, and tools (i.e., software and databases). RRIDs are assigned by an authoritative database, for example, a model organism database for each type of resource. To make it easier for authors to obtain RRIDs, resources were aggregated from the appropriate databases and their RRIDs made available in a central web portal (http://scicrunch.org/resources). RRIDs meet three key criteria: they are machine readable, free to generate and access, and are consistent across publishers and journals. The pilot was launched in February of 2014 and over 300 papers have appeared that report RRIDs. The number of journals participating has expanded from the original 25 to more than 40 with RRIDs appearing in 62 different journals to date. Here, we present an overview of the pilot project and its outcomes to date. We show that authors are able to identify resources and are supportive of the goals of the project. Identifiability of the resources post-pilot showed a dramatic improvement for all three resource types, suggesting that the project has had a significant impact on identifiability of research resources. Resource Identification Initiative was launched as a pilot project to improve the reporting standards for research resources in the methods sections of papers and thereby improve identifiability and reproducibility. Here, we present an overview of

the pilot project and its outcomes to date. We show that authors are generally accurate in performing the task of identifying resources and supportive of the goals of the project. © 2015 Published by Wiley Periodicals, Inc.

Barnard, R. A., Pomaville, M. B., & O'Roak, B. J. (2015). Mutations and modeling of the chromatin remodeler CHD8 define an emerging autism etiology. *Frontiers in Neuroscience, 9*, 477. Autism Spectrum Disorder (ASD) is a common neurodevelopmental disorder with a strong but complex genetic component. Recent family based exome-sequencing strategies have identified recurrent de novo mutations at specific genes, providing strong evidence for ASD risk, but also highlighting the extreme genetic heterogeneity of the disorder. However, disruptions in these genes converge on key molecular pathways early in development. In particular, functional enrichment analyses have found that there is a bias toward genes involved in transcriptional regulation, such as chromatin modifiers. Here we review recent genetic, animal model, co-expression network, and functional genomics studies relating to the high confidence ASD risk gene, CHD8. CHD8, a chromatin remodeling factor, may serve as a "master regulator" of a common ASD etiology. Individuals with a CHD8 mutation show an ASD subtype that includes similar physical characteristics, such as macrocephaly and prolonged GI problems including recurrent constipation. Similarly, animal models of CHD8 disruption exhibit enlarged head circumference and reduced gut motility phenotypes. Systems biology approaches suggest CHD8 and other candidate ASD risk genes are enriched during mid-fetal development, which may represent a critical time window in ASD etiology. Transcription and CHD8 binding site profiles from cell and primary tissue models of early development indicate that CHD8 may also positively regulate other candidate ASD risk genes through both direct and indirect means. However, continued study is needed to elucidate the mechanism of regulation as well as identify which CHD8 targets are most relevant to ASD risk. Overall, these initial studies suggest the potential for common ASD etiologies and the development of personalized treatments in the future.

Beadling, C., Wald, A. I., Warrick, A., Neff, T. L., Zhong, S., Nikiforov, Y. E., et al. (2015). A multiplexed amplicon approach for detecting gene fusions by next-generation sequencing. *The Journal of Molecular Diagnostics : JMD,*

Chromosomal rearrangements that result in oncogenic gene fusions are clinically important drivers of many cancer types. Rapid and sensitive methods are therefore needed to detect a broad range of gene fusions in clinical specimens that are often of limited quantity and quality. We describe a next-generation sequencing approach that uses a multiplex PCR-based amplicon panel to interrogate fusion transcripts that involve 19 driver genes and 94 partners implicated in solid tumors. The panel also includes control assays that evaluate the 3'/5' expression ratios of 12 oncogenic kinases, which might be used to infer gene fusion events when the partner is unknown or not included on the panel. There was good concordance between the solid tumor fusion gene panel and other methods, including fluorescence in situ hybridization, real-time PCR, Sanger sequencing, and other next-generation sequencing panels, because 40 specimens known to harbor gene fusions were correctly identified. No specific fusion reads were observed in 59 fusion-negative specimens. The 3'/5' expression ratio was informative for fusions that involved ALK, RET, and NTRK1 but not for BRAF or ROS1 fusions. However, among 37 ALK or RET fusion-negative specimens, four exhibited elevated 3'/5' expression ratios, indicating that fusions predicted solely by 3'/5' read ratios require confirmatory testing.

Beattie, Z. T., Jacobs, P. G., Riley, T. C., & Hagen, C. C. (2015). A time-frequency respiration tracking system using non-contact bed sensors with harmonic artifact rejection. *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2015, , 2015-November.* pp. 8111-8114.

Sleep apnea is a breathing disorder that affects many individuals and has been associated with serious health conditions such as cardiovascular disease. Clinical diagnosis of sleep apnea requires that a patient spend the night in a sleep clinic while being wired up to numerous obtrusive sensors. We are developing a system that utilizes respiration rate and breathing amplitude inferred from non-contact bed sensors (i.e. load cells placed under bed supports) to detect sleep apnea. Multi-harmonic artifacts generated either biologically or as a result of the impulse response of the bed have made it challenging to track respiration rate and amplitude with high resolution in time. In this paper, we present an algorithm that can accurately track respiration on a second-by-second basis while removing noise harmonics. The algorithm is tested using data collected from 5 patients during overnight sleep studies. Respiration rate is compared

with polysomnography estimations of respiration rate estimated by a technician following clinical standards. Results indicate that certain subjects exhibit a large harmonic component of their breathing signal that can be removed by our algorithm. When compared with technician transcribed respiration rates using polysomnography signals, we demonstrate improved accuracy of respiration rate tracking using harmonic artifact rejection (mean error: 0.18 breaths/minute) over tracking not using harmonic artifact rejection (mean error: -2.74 breaths/minute). © 2015 IEEE.

Beauchamp, G. A., McKeown, N. J., Rodriguez, S., & Spyker, D. A. (2016). Relating calls to US poison centers for potential exposures to medications to centers for disease control and prevention reporting of influenza-like illness. *Clinical Toxicology (Philadelphia, Pa.),* , 1-6.
CONTEXT: The Centers for Disease Control (CDC) monitors influenza like illness (ILI) and the National Poison Data System (NPDS) warehouses call data uploaded by US poison centers regarding reported exposures to medication. OBJECTIVE: We examined the relationship between calls to poison centers regarding reported exposures to medications commonly used to treat ILI and weekly reports of ILI. MATERIALS AND METHODS: The CDC reports ILI, by age group, for each of 10 Health and Human Services (HHS) regions. We examined NPDS summary data from calls reported to poison centers regarding reported exposures to acetaminophen, cough/cold medications, and promethazine, for the same weeks, age groups, and HHS regions for influenza seasons 2000-2013. ILI and NPDS exposures were examined using graphical plots, descriptive statistics, stepwise regression analysis, and Geographic Information Systems (GIS). RESULTS: About 5,101,841 influenza-like illness cases were reported to the CDC, and 2,122,940 calls regarding reported exposures to medications commonly used to treat ILI, were reported by poison centers to the NPDS over the 13 flu seasons. Analysis of stepwise models of the linear untransformed data involving 24 NPDS data groups and for 60 ILI measures, over the 13 influenza seasons, demonstrated that reported exposures to medications used to treat ILI correlated with reported cases of ILI with a median R2 = 0.489 (min R2 = 0.248, max R2 = 0.717), with mean +/- SD of R2 = 0.494 +/- 0.121. Median number of parameters used (degrees of freedom - 1) was 7. CONCLUSIONS: NPDS data regarding poison center calls for selected ILI medication exposures were highly correlated with CDC ILI data. Since NPDS data are available in

real time, it provides complimentary ILI monitoring. This approach may provide public health value in predicting other illnesses which are not currently as thoroughly monitored.

Bellmore, R. A., Harrison, J. A., Needoba, J. A., Brooks, E. S., & Kent Keller, C. (2015). Hydrologic control of dissolved organic matter concentration and quality in a semiarid artificially drained agricultural catchment. *Water Resources Research,*

Agricultural practices have altered watershed-scale dissolved organic matter (DOM) dynamics, including in-stream concentration, biodegradability, and total catchment export. However, mechanisms responsible for these changes are not clear, and field-scale processes are rarely directly linked to the magnitude and quality of DOM that is transported to surface water. In a small (12 ha) agricultural catchment in eastern Washington State, we tested the hypothesis that hydrologic connectivity in a catchment is the dominant control over the concentration and quality of DOM exported to surface water via artificial subsurface drainage. Concentrations of dissolved organic carbon (DOC) and humic-like components of DOM decreased while the Fluorescence Index and Freshness Index increased with depth through the soil profile. In drain discharge, these characteristics were significantly correlated with drain flow across seasons and years, with drain DOM resembling deep sources during low-flow and shallow sources during high flow, suggesting that DOM from shallow sources bypasses removal processes when hydrologic connectivity in the catchment is greatest. Assuming changes in streamflow projected for the Palouse River (which contains the study catchment) under the A1B climate scenario (rapid growth, dependence on fossil fuel, and renewable energy sources) apply to the study catchment, we project greater interannual variability in annual DOC export in the future, with significant increases in the driest years. This study highlights the variability in DOM inputs from agricultural soil to surface water on daily to interannual time scales, pointing to the need for a more nuanced understanding of agricultural impacts on DOM dynamics in surface water.

Berry, S. A., Ghanem, K. G., Mathews, W. C., Korthuis, P. T., Yehia, B. R., Agwu, A. L., et al. (2015). Brief report: Gonorrhea and chlamydia testing increasing but still lagging in HIV clinics in the united states. *Journal of Acquired Immune Deficiency Syndromes (1999), 70*(3), 275-279.

Screening persons living with HIV for gonorrhea and chlamydia has been recommended since 2003. We compared annual gonorrhea/chlamydia testing to syphilis and lipid testing among 19,368 adults (41% men who have sex with men, 30% heterosexual men, and 29% women) engaged in HIV care. In 2004, 22%, 62%, and 70% of all patients were tested for gonorrhea/chlamydia, syphilis, and lipid levels, respectively. Despite increasing steadily [odds ratio per year (95% confidence interval): 1.14 (1.13 to 1.15)], gonorrhea/chlamydia testing in 2010 remained lower than syphilis and lipid testing (39%, 77%, 76%, respectively). Interventions to improve gonorrhea/chlamydia screening are needed. A more targeted screening approach may be warranted.

Best, K. M., Asaro, L. A., Franck, L. S., Wypij, D., Curley, M. A. Q., Allen, G. L., et al. (2016). Patterns of sedation weaning in critically ill children recovering from acute respiratory failure. *Pediatric Critical Care Medicine, 17*(1), 19-29.

Objective: To characterize sedation weaning patterns in typical practice settings among children recovering from critical illness. Design: A descriptive secondary analysis of data that were prospectively collected during the prerandomization phase (January to July 2009) of a clinical trial of sedation management. Setting: Twenty-two PICUs across the United States. Patients: The sample included 145 patients, aged 2 weeks to 17 years, mechanically ventilated for acute respiratory failure who received at least five consecutive days of opioid exposure. Interventions: None. Measurements and Main Results: Group comparisons were made between patients with an intermittent weaning pattern, defined as a 20% or greater increase in daily opioid dose after the start of weaning, and the remaining patients defined as having a steady weaning pattern. Demographic and clinical characteristics, tolerance to sedatives, and iatrogenic withdrawal symptoms were evaluated. Sixty-six patients (46%) were intermittently weaned; 79 patients were steadily weaned. Prior to weaning, intermittently weaned patients received higher peak and cumulative doses and longer exposures to opioids and benzodiazepines, demonstrated more sedative tolerance (58% vs 41%), and received more chloral hydrate and barbiturates compared with steadily weaned patients. During weaning, intermittently weaned patients assessed for withdrawal had a higher incidence of Withdrawal Assessment Tool-version 1 scores of greater than or equal to 3 (85% vs 46%) and received more sedative classes compared with steadily

weaned patients. Conclusions: This study characterizes sedative administration practices for pediatric patients prior to and during weaning from sedation after critical illness. It provides a novel methodology for describing weaning in an at-risk pediatric population that may be helpful in future research on weaning strategies to prevent iatrogenic withdrawal syndrome.

Bishop, C. V., Xu, F., Molskness, T. A., Stouffer, R. L., & Hennebold, J. D. (2015). Dynamics of immune cell types within the macaque corpus luteum during the menstrual cycle: Role of progesterone. *Biology of Reproduction, 93*(5)

The goal of the current study was to characterize the immune cell types within the primate corpus luteum (CL). Luteal tissue was collected from rhesus females at discrete intervals during the luteal phase of the natural menstrual cycle. Dispersed cells were incubated with fluorescently labeled antibodies specific for the immune cell surface proteins CD11b (neutrophils and monocytes/macrophages), CD14 (monocytes/macrophages), CD16 (natural killer [NK] cells), CD20 (B-lymphocytes), and CD3epsilon (T-lymphocytes) for analysis by flow cytometry. Numbers of CD11b-positive (CD11b+) and CD14+ cells increased significantly 3 to 4 days after serum progesterone (P4) concentrations declined below 0.3 ng/ml. CD16+ cells were the most abundant immune cell type in CL during the mid and mid-late luteal phases and were 3-fold increased 3 to 4 days after serum P4 decreased to baseline levels. CD3epsilon+ cells tended to increase 3 to 4 days after P4 decline. To determine whether immune cells were upregulated by the loss of luteotropic (LH) support or through loss of LH-dependent steroid milieu, monkeys were assigned to 4 groups: control (no treatment), the GnRH antagonist Antide, Antide plus synthetic progestin (R5020), or Antide plus the estrogen receptor agonists diarylpropionitrile (DPN)/propyl-pyrazole-triol (PPT) during the mid-late luteal phase. Antide treatment increased the numbers of CD11b+ and CD14+ cells, whereas progestin, but not estrogen, replacement suppressed the numbers of CD11b+, CD14+, and CD16+ cells. Neither Antide nor steroid replacement altered numbers of CD3epsilon+ cells. These data suggest that increased numbers of innate immune cells in primate CL after P4 synthesis declines play a role in onset of structural regression of primate CL.

Bishop, C. V., Xu, F., Xu, J., Ting, A. Y., Galbreath, E., McGee, W. K., et al. (2015). Western-style diet, with and without chronic androgen treatment, alters the number, structure, and function of small antral follicles in ovaries of young adult monkeys. *Fertility and Sterility,*
Objective: To examine the small antral follicle (SAF) cohort in ovaries of adult rhesus monkeys after consumption of a Western-style diet (WSD), with or without chronically elevated androgen levels since before puberty. Design: Cholesterol or T (n = 6 per group) implants were placed SC in female rhesus macaques beginning at 1 year of age (prepubertal), with addition of a WSD (high fat/fructose) at 5.5 years (menarche approximately 2.6 years). Ovaries were collected at 7 years of age. One ovary per female was embedded in paraffin for morphologic and immunohistochemical analyses. The SAFs (<2.5 mm) were dissected from the other ovary obtained at or near menses in a subgroup of females (n = 3 per group) and processed for microarray analyses of the SAF transcriptome. Ovaries of adult monkeys consuming a standard macaque diet (low in fats and sugars) were obtained at similar stages of the menstrual cycle and used as controls for all analyses. Setting: Primate research center. Animal(s): Adult, female rhesus monkeys (Macaca mulatta). Intervention(s): None. Main Outcome Measures: Histologic analyses, SAF counts and morphology, protein localization and abundance in SAFs, transcriptome in SAFs (messenger RNAs [mRNAs]). Result(s): Compared with controls, consumption of a WSD, with and without T treatment, increased the numbers of SAFs per ovary, owing to the presence of more atretic follicles. Numbers of granulosa cells expressing cellular proliferation markers (pRb and pH3) was greater in healthy SAFs, whereas numbers of cells expressing the cell cycle inhibitor (p21) was higher in atretic SAFs. Intense CYP17A1 staining was observed in the theca cells of SAFs from WSD with or without T groups, compared with controls. Microarray analyses of the transcriptome in SAFs isolated from WSD and WSD plus T-treated females and controls consuming a standard diet identified 1,944 genes whose mRNA levels changed twofold or more among the three groups. Further analyses identified several gene pathways altered by WSD and/or WSD plus T associated with steroid, carbohydrate, and lipid metabolism, plus ovarian processes. Alterations in levels of several SAF mRNAs are similar to those observed in follicular cells from women with polycystic ovary syndrome. Conclusion(s): These data indicate that consumption of a WSD high in fats and sugars in the presence and absence of chronically

elevated T alters the structure and function of SAFs within primate ovaries. © 2015 American Society for Reproductive Medicine.

Blaha, M. J., Cainzos-Achirica, M., Greenland, P., McEvoy, J. W., Blankstein, R., Budoff, M. J., et al. (2016). Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: The multi-ethnic study of atherosclerosis (MESA). *Circulation,* BACKGROUND: -Limited attention has been paid to negative cardiovascular disease (CVD) risk markers despite their potential to improve medical decision-making. We compared thirteen negative risk markers using diagnostic likelihood ratios (DLR), which model the change in risk for an individual after the result of an additional test. METHODS AND RESULTS: -We examined 6,814 participants from the Multi-Ethnic Study of Atherosclerosis. Coronary artery calcium (CAC) =0, carotid intima-media thickness (CIMT) 5% change, ankle brachial index (ABI) >0.9 and 5% change, ankle brachial index (ABI) >0.9 and 5% change, ankle brachial index (ABI) >0.9 and 5% change, ankle brachial index (ABI) >0.9 and 5% change, ankle brachial index (ABI) >0.9 and 5% change, ankle brachial index (ABI) >0.9 and 0.80. Among clinical features, absence of any family history of CHD was the strongest (DLRs 0.76 [0.07] and 0.81 [0.06], respectively). Net Reclassification Improvement (NRI) analyses yielded similar findings, with CAC=0 resulting in the largest, most accurate downward risk reclassification. CONCLUSIONS: -Negative results of atherosclerosis-imaging tests, particularly CAC=0, resulted in the greatest downward shift in estimated CVD risk. These results may help guide discussions regarding identification of individuals less likely to receive net benefit from lifelong preventive pharmacotherapy.

Bleyer, A. (2015). Letter to the editor: Management of concurrent pregnancy and acute lymphoblastic leukemia or lymphoblastic lymphoma. comment on the article by zaidi et al. *Journal of Adolescent and Young Adult Oncology, 4*(2), 91-92.

Bornstein, S., Schmidt, M., Choonoo, G., Levin, T., Gray, J., Thomas, C. R.,Jr, et al. (2016). IL-10 and integrin signaling pathways are associated with head and neck cancer progression. *BMC Genomics, 17*(1), 38-015-2359-6.
BACKGROUND: Head and neck cancer is morbid with a poor prognosis that has not significantly improved in the past several decades. The purpose of this study was to identify biological

pathways underlying progressive head and neck cancer to inform prognostic and adjuvant strategies. We identified 235 head and neck cancer patients in The Cancer Genome Atlas (TCGA) with sufficient clinical annotation regarding therapeutic treatment and disease progression to identify progressors and non-progressors. We compared primary tumor gene expression and mutational status between these two groups. RESULTS: 105 genes were differentially expressed between progressors and nonprogressors (FDR < 0.05). Pathway analyses revealed deregulation (FDR < 0.05) of multiple pathways related to integrin signaling as well as IL-10 signaling. A number of genes were uniquely mutated in the progressor cohort including increased frequency of truncating mutations in CTCF (P = 0.007). An 11-gene signature derived from a combination of unique mutations and differential expression was identified (PAGE4, SMTNL1, VTN, CA5A, C1orf43, KRTAP19-1, LEP, HRH4, PAGE5, SEZ6L, CREB3). This signature was associated with decreased overall survival (Logrank Test; P = 0.03443). Cox modeling of both key clinical features and the signature was significant (P = 0.032) with the greatest prognostic improvement seen in the model based on nodal extracapsular spread and alcohol use alone (P = 0.004). CONCLUSIONS: Molecular analyses of head and neck cancer tumors that progressed despite treatment, identified IL-10 and integrin pathways to be strongly associated with cancer progression. In addition, we identified an 11-gene signature with implications for patient prognostication. Mutational analysis highlighted a potential role for CTCF, a crucial regulator of long-range chromatin interactions, in head and neck cancer progression.

Borschewski, A., Himmerkus, N., Boldt, C., Blankenstein, K. I., McCormick, J. A., Lazelle, R., et al. (2016). Calcineurin and sorting-related receptor with A-type repeats interact to regulate the renal na+-K+-2Cl- cotransporter. *Journal of the American Society of Nephrology, 27*(1), 107-119.
The furosemide-sensitive Na+-K+-2Cl--cotransporter (NKCC2) is crucial for NaCl reabsorption in kidney thick ascending limb (TAL) and drives the urine concentrating mechanism. NKCC2 activity ismodulated by N-terminal phosphorylation and dephosphorylation. Serine-threonine kinases that activate NKCC2 have been identified, but less is known about phosphatases that deactivate NKCC2. Inhibition of calcineurin phosphatase has been shown to stimulate transport in the TAL and the distal convoluted tubule. Here, we identified NKCC2 as a target of the calcineurin Aβ isoform. Short-term cyclosporine administration inmice augmented the abundance of phospho-

NKCC2, and treatment of isolated TAL with cyclosporine increased the chloride affinity and transport activity of NKCC2. Because sorting-related receptor with Atype repeats (SORLA) may affect NKCC2 phosphoregulation, we used SORLA-knockout mice to test whether SORLA is involved in calcineurin-dependent modulation of NKCC2. SORLA-deficient mice showed more calcineurin Aβ in the apical region of TAL cells and less NKCC2 phosphorylation and activity compared with littermate controls. In contrast, overexpression of SORLA in cultured cells reduced the abundance of endogenous calcineurin Aβ. Cyclosporine administration rapidly normalized the abundance of phospho-NKCC2 in SORLA-deficientmice, and a functional interaction between calcineurin Aβ and SORLAwas further corroborated by binding assays in rat kidney extracts. In summary, we have shown that calcineurin Aβ and SORLA are key components in the phosphoregulation of NKCC2. These results may have clinical implications for immunosuppressive therapy using calcineurin inhibitors. © 2016 by the American Society of Nephrology.

Bourdette, D., & Hartung, D. (2015). Equivalence of glatiramer acetate generics with branded glatiramer acetate in efficacy and cost for the treatment of multiple sclerosis. *JAMA Neurology, 72*(12), 1411-1413.

Bressler, S. B., Ayala, A. R., Bressler, N. M., Melia, M., Qin, H., Ferris, F. L.,3rd, et al. (2016). Persistent macular thickening after ranibizumab treatment for diabetic macular edema with vision impairment. *JAMA Ophthalmology,* , 1-8.

Importance: The prevalence of persistent diabetic macular edema (DME) after months of anti-vascular endothelial growth factor therapy and its effect on visual acuity are unknown. Objective: To assess subsequent outcomes of eyes with DME persisting for 24 weeks after initiating treatment with 0.5 mg of ranibizumab. Design, Setting, and Participants: We performed post hoc, exploratory analyses of a randomized clinical trial from March 20, 2007, through January 29, 2014, from 117 of 296 eyes (39.5%) randomly assigned to receive ranibizumab with persistent DME (central subfield thickness >/=250 mum on time domain optical coherence tomography) through the 24-week visit. Interventions: Four monthly intravitreous injections of ranibizumab and then as needed per protocol. Main Outcomes and Measures: Cumulative 3-year probabilities of chronic persistent DME (failure to achieve a central subfield thickness /=2 line) gain or loss of

visual acuity among those eyes. Results: The probability of chronic persistent DME among eyes with persistent DME at the 24-week visit decreased from 100% at the 32-week visit to 81.1% (99% CI, 69.6%-88.6%), 55.8% (99% CI, 42.9%-66.9%), and 40.1% (99% CI, 27.4%-52.4%) at the 1-, 2-, and 3-year visits, respectively. At 3 years, visual acuity improved in eyes with and without chronic persistent DME through the follow-up period, respectively, by a mean of 7 letters and 13 letters from baseline. Among 40 eyes with chronic persistent edema through 3 years, 17 (42.5%) (99% CI, 23.1%-63.7%) gained 10 letters or more from baseline, whereas 5 (12.5%) (99% CI, 2.8%-31.5%) lost 10 letters or more from baseline. Conclusions and Relevance: These data suggest less than half of eyes treated for DME with intravitreous ranibizumab have persistent central-involved DME through 24 weeks after initiating treatment. Among the 40% that then have chronic persistent central-involved DME through 3 years, longer-term visual acuity outcomes appear to be slightly worse than in the 60% in which DME does not persist. Nevertheless, when following the treatment protocol used in this trial among eyes with vision impairment from DME, long-term improvement in visual acuity from baseline is typical and substantial (>/=2-line) loss of visual acuity is likely uncommon through 3 years, even when central-involved DME chronically persists.

Broberg, C. S., Huang, J., Hogberg, I., McLarry, J., Woods, P., Burchill, L. J., et al. (2016). Diffuse LV myocardial fibrosis and its clinical associations in adults with repaired tetralogy of fallot. *JACC: Cardiovascular Imaging, 9*(1), 86-87.

Burton, K. J., Li, X., Li, B., Cheng, M. Y., Urbanski, H. F., & Zhou, Q. Y. (2016). Expression of prokineticin 2 and its receptor in the macaque monkey brain. *Chronobiology International,* , 1-9. Prokineticin 2 (PK2) has been indicated as an output signaling molecule for the suprachiasmatic nucleus (SCN) circadian clock. Most of these studies were performed with nocturnal animals, particularly mice and rats. In the current study, the PK2 and its receptor, PKR2, was cloned from a species of diurnal macaque monkey. The macaque monkey PK2 and PKR2 were found to be highly homologous to that of other mammalian species. The mRNA expression of PK2 and PKR2 in the macaque brain was examined by in situ hybridization. The expression patterns of PK2 and PKR2 in the macaque brain were found to be quite similar to that of the mouse brain. Particularly,

PK2 mRNA was shown to oscillate in the SCN of the macaque brain in the same phase and with similar amplitude with that of nocturnal mouse brain. PKR2 expression was also detected in known primary SCN targets, including the midline thalamic and hypothalamic nuclei. In addition, we detected the expression of PKR2 mRNA in the dorsal raphe nucleus (DR) of both macaque and mouse brains. As a likely SCN to dorsal raphe projection has previously been indicated, the expression of PKR2 in the raphe nuclei of both macaque and mouse brain signifies a possible role of DR as a previously unrecognized primary SCN projection target.

Butler, M. W. (2015). Developing pediatric surgery in low- and middle-income countries: An evaluation of contemporary education and care delivery models. *Seminars in Pediatric Surgery,*

There are several different models of education and care delivery models in low- and middle-income countries (LMICs), and many endeavors combine more than one of the described models. This article summarizes the burden of pediatric surgical disease and discusses the benefits and shortcomings of the following: faith-based missions; short-term surgical trips; partnerships, twinning, and academic collaborations; teaching workshops, "train the trainer," and pediatric surgery camps; specialty treatment centers; online conferences, telemedicine, and mobile health; specific programs for exchange and education; and training in high-income countries (HICs), fellowships, and observorships. It then addresses ethical concerns common to all humanitarian pediatric surgical efforts.

Butler-Dawson, J., Galvin, K., Thorne, P. S., & Rohlman, D. S. (2016). Organophosphorus pesticide exposure and neurobehavioral performance in latino children living in an orchard community. *Neurotoxicology,*

Children living in agricultural communities have a greater risk from pesticides due to para-occupational pathways. The goal of this study was to assess the impact of exposure to organophosphorus pesticides on the neurobehavioral performance of school-aged Latino children over time. Two exposure measures were used to estimate children's pesticide exposure: parent's occupation (agricultural or non-agricultural) and organophosphate residues in home carpet dust samples. During 2008-2011, 206 school-aged children completed a battery of neurobehavioral tests two times, approximately one year apart. The associations between both exposure

measures and neurobehavioral performance were examined. Pesticide residues were detected in dust samples from both agricultural and non-agricultural homes, however, pesticides were detected more frequently and in higher concentrations in agricultural homes compared to non-agricultural homes. Although few differences were found between agricultural and non-agricultural children at both visits, deficits in learning from the first visit to the second visit, or less improvement, was found in agricultural children relative to non-agricultural children. These differences were significant for the Divided Attention and Purdue Pegboard tests. These findings are consistent with previous research showing deficits in motor function. A summary measure of organophosphate residues was not associated with neurobehavioral performance. Results from this study indicate that children in agricultural communities are at increased risk from pesticides as a result of a parent working in agricultural. Our findings suggest that organophosphate exposure may be associated with deficits in learning on neurobehavioral performance, particularly in tests of with motor function. In spite of regulatory phasing out of organophosphates in the U.S., we still see elevated levels and higher detection rates of several organophosphates in agricultural households than non-agricultural households, albeit lower levels than prior studies.

Cabrera, I. E., Pacentine, I. V., Lim, A., Guerrero, N., Krystofova, S., Li, L., et al. (2015). Global analysis of predicted G protein-coupled receptor genes in the filamentous fungus, neurospora crassa. *G3: Genes, Genomes, Genetics, 5*(12), 2729-2743.

Gprotein-coupled receptors (GPCRs) regulate facets of growth, development, and environmental sensing in eukaryotes, including filamentous fungi. The largest predicted GPCR class in these organisms is the Pth11-related, with members similar to a protein required for disease in the plant pathogen Magnaporthe oryzae. However, the Pth11-related class has not been functionally studied in any filamentous fungal species. Here, we analyze phenotypes in available mutants for 36 GPCR genes, including 20 Pth11-related, in the model filamentous fungus Neurospora crassa. We also investigate patterns of gene expression for all 43 predicted GPCR genes in available datasets. A total of 17 mutants (47%) possessed at least one growth or developmental phenotype. We identified 18 mutants (56%) with chemical sensitivity or nutritional phenotypes (11 uniquely), bringing the total number of mutants with at least one defect to 28 (78%), including 15 mutants (75%) in the Pth11-related class. Gene expression trends for GPCR genes

correlated with the phenotypes observed for many mutants and also suggested overlapping functions for several groups of co-transcribed genes. Several members of the Pth11-related class have phenotypes and/or are differentially expressed on cellulose, suggesting a possible role for this gene family in plant cell wall sensing or utilization. © 2015 Cabrera et al.

Canavero, I., Sherburne, H. A., Tremble, S. M., Clark, W. M., & Cipolla, M. J. (2016). Effects of acute stroke serum on non-ischemic cerebral and mesenteric vascular function. *Translational Stroke Research,*

We investigated the effects of circulating factors in serum obtained from patients in the acute phase of different subtypes of ischemic stroke on non-ischemic cerebral and mesenteric arteries, as a potential mechanism involved in influencing regional perfusion and thus clinical evolution. Posterior cerebral arteries (PCAs) and mesentery arteries (MAs) isolated from Wistar Kyoto rats were perfused with serum from acute stroke patients with large vessel disease without (LVD) or with hypertension (LVD + HTN), cardioembolism with hypertension (CE + HTN), or physiologic saline as controls. Myogenic activity and nitric oxide-dependent vasorelaxation were assessed after 2 h of intraluminal exposure to serum. Vascular function was differentially affected by sera. Exposure to LVD serum increased myogenic tone and produced endothelial dysfunction in both PCAs and MAs. However, CE + HTN serum increased tone and decreased smooth muscle sensitivity to NO in vessels from both vascular beds. LVD + HTN serum was associated with reduced smooth muscle sensitivity to NO in vessels from both vascular beds but increased tone only in PCAs. Inflammation and oxidative stress, determined by measurement of high sensitivity C-reactive protein, uric acid, and free 8-isoprostane, were enhanced in all the serum groups. These results demonstrate vasoactive properties of acute stroke serum related to stroke subtypes that could potentially contribute to the pathogenesis of early hemodynamic-based clinical events.

Carney, P. A., Palmer, R. T., Fuqua Miller, M., Thayer, E. K., Estroff, S. E., Litzelman, D. K., et al. (2016). Tools to assess behavioral and social science competencies in medical education: A systematic review. *Academic Medicine : Journal of the Association of American Medical Colleges,* PURPOSE: Behavioral and social science (BSS) competencies are needed to provide quality health care, but psychometrically validated measures to assess these competencies are difficult to find.

Moreover, they have not been mapped to existing frameworks, like those from the Liaison Committee on Medical Education (LCME) and Accreditation Council for Graduate Medical Education (ACGME). This systematic review aimed to identify and evaluate the quality of assessment tools used to measure BSS competencies. METHOD: The authors searched the literature published between January 2002 and March 2014 for articles reporting psychometric or other validity/reliability testing, using OVID, CINAHL, PubMed, ERIC, Research and Development Resource Base, SOCIOFILE, and PsycINFO. They reviewed 5,104 potentially relevant titles and abstracts. To guide their review, they mapped BSS competencies to existing LCME and ACGME frameworks. The final included articles fell into three categories: instrument development, which were of the highest quality; educational research, which were of the second highest quality; and curriculum evaluation, which were of lower quality. RESULTS: Of the 114 included articles, 33 (29%) yielded strong evidence supporting tools to assess communication skills, cultural competence, empathy/compassion, behavioral health counseling, professionalism, and teamwork. Sixty-two (54%) articles yielded moderate evidence and 19 (17%) weak evidence. Articles mapped to all LCME standards and ACGME core competencies; the most common was communication skills. CONCLUSIONS: These findings serve as a valuable resource for medical educators and researchers. More rigorous measurement validation and testing and more robust study designs are needed to understand how educational strategies contribute to BSS competency development.

Carpenter, D. M., Geryk, L. L., Chen, A. T., Nagler, R. H., Dieckmann, N. F., & Han, P. K. J. (2015). Conflicting health information: A critical research need. *Health Expectations,*

Conflicting health information is increasing in amount and visibility, as evidenced most recently by the controversy surrounding the risks and benefits of childhood vaccinations. The mechanisms through which conflicting information affects individuals are poorly understood; thus, we are unprepared to help people process conflicting information when making important health decisions. In this viewpoint article, we describe this problem, summarize insights from the existing literature on the prevalence and effects of conflicting health information, and identify important knowledge gaps. We propose a working definition of conflicting health information and describe a conceptual typology to guide future research in this area. The typology classifies

conflicting information according to four fundamental dimensions: the substantive issue under conflict, the number of conflicting sources (multiplicity), the degree of evidence heterogeneity and the degree of temporal inconsistency. © 2015 John Wiley & Sons Ltd.

Cassidy, P. B., Leachman, S. A., & Moos, P. J. (2015). In Preedy V.R. (Ed.), *Selenium and skin cancer* Royal Society of Chemistry.

Melanoma and the nonmelanoma skin cancers arise from normal cells in the epithelial layer of the skin. Risk factors for skin cancers are complex and involve numerous inherited, environmental, and biological factors including selenoproteins that are involved in the response of the skin to UV-induced oxidative stress. Results from epidemiological studies of dietary, environmental, and supplemental sources of selenium suggest that in some cases selenium reduces, but in other cases increases, the risk for skin cancer in humans. Studies in model systems using compounds that can enter the "central selenium pool", thereby supporting the synthesis of selenoproteins, have also been mixed. It seems likely that there is a U-shaped curve for selenium intake and skin cancer risk, where the risk is highest at both deficient (<20 μg per day) and supranutritional levels. © The Royal Society of Chemistry 2015.

Caughey, A. B. (2016). Racial and ethnic disparities in general anesthesia for cesarean: What are the implications? *Anesthesia and Analgesia, 122*(2), 297-298.

Cawthon, P. M., Shahnazari, M., Orwoll, E. S., & Lane, N. E. (2016). Osteoporosis in men: Findings from the osteoporotic fractures in men study (MrOS). *Therapeutic Advances in Musculoskeletal Disease, 8*(1), 15-27.

The lifespan of men is increasing and this is associated with an increased prevalence of osteoporosis in men. Osteoporosis increases the risk of bone fracture. Fractures are associated with increased disability and mortality, and public health problems. We review here the study of osteoporosis in men as obtained from a longitudinal cohort of community-based older men, the Osteoporotic Fractures in Men Study (MrOS). © 2015, © The Author(s), 2015.

Charry, J. D., Rubiano, A. M., Nikas, C. V., Ortíz, J. C., Puyana, J. C., Carney, N., et al. (2016). Results of early cranial decompression as an initial approach for damage control therapy in

severe traumatic brain injury in a hospital with limited resources. *Journal of Neurosciences in Rural Practice, 7*(1), 7-12.

Introduction: Severe traumatic brain injury (sTBI) is a disease that generates significant mortality and disability in Latin America, and specifically in Colombia. The purpose of this study was to evaluate the 12-month clinical outcome in patients with sTBI managed with an early cranial decompression (ECD) as the main procedure for damage control (DC) therapy, performed in a University Hospital in Colombia over a 4-year period. Materials and Methods: A database of 106 patients who received the ECD procedure, and were managed according to the strategy for DC in neurotrauma, was analyzed. Variables were evaluated, and the patient outcome was determined according to the Glasgow Outcome Score (GOS) at 12 months postinjury. This was used to generate a dichotomous variable with 'favorable' (GOS of 4 or 5) or 'unfavorable' (GOS of 1-3) outcomes; analysis of variance was performed with the Chi-square, Wilcoxon-Mann-Whitney and Fisher tests. Results: An overall survival rate of 74.6% was observed for the procedure, At 12 months postsurgery, a favorable clinical outcome (GOS 4-5) was found in 70 patients (66.1%), Unfavorable outcomes in patients were associated with the following factors: Closed trauma, an Injury Severity Score >16 , obliterated basal cisterns, subdural hematoma as the main injury seen on the admission computed tomography, and nonreactive pupils observed in the emergency department. Conclusion: Twelve months outcome of patients with sTBI managed with ECD in a neuromonitoring limited resource University Hospital in Colombia shows an important survival rate with favorable clinical outcome measure with GOS.

Chen, G., & Palmer, E. (2014). Fibromyalgia and opioid-induced hyperalgesia. (pp. 214-222) Cambridge University Press.

A 45-year-old woman was referred to a pain management center from her primary care doctor’s office for evaluation and treatment of her fibromyalgia. Per history, patient complains of worsening fatigue, headache, and widespread and migrating pain all over her body. She relates that the pain is most bothersome in her shoulders and lower back but is also present in her thoracic spine, neck, right elbow, and bilaterally in her knees. She remembers having diffuse body pain since age 25 when she got into a motor vehicle accident in which her car was wrecked even though she did not have any fractures or hospitalization from that accident. On further

evaluation, she has also been dealing with depression and insomnia. She does not think that she has fibromyalgia and she would like to have a different diagnosis and be cured of her pain. She also would like to increase her opioid dosage as her pain has worsened since her son had gone to college. 1. What is the differential diagnosis? Some differential diagnoses for widespread body pain include: Fibromyalgia Polymyalgia rheumatica Myositis/myopathies Myofascial pain syndrome Rheumatoid arthritis Systemic lupus erythematosis Sjogren's syndrome Ankylosing spondylitis Hypothyroidism Somatoform disorder Cervical spinal stenosis Systemic vasculitis. © Cambridge University Press 2015.

Chen, S., Whitson, H., Quiñones, A., & Thielke, S. (2015). Comparative health and self-rated health are equivalently associated with health indicators among older adults. *Journal of Clinical Epidemiology,*

Chernov, M. M., Chen, G., Torre-Healy, L. A., Friedman, R. M., & Roe, A. W. (2016). Microelectrode array stimulation combined with intrinsic optical imaging: A novel tool for functional brain mapping. *Journal of Neuroscience Methods,*

BACKGROUND: Functional brain mapping via cortical microstimulation is a widely used clinical and experimental tool. However, data are traditionally collected point by point, making the technique very time consuming. Moreover, even in skilled hands, consistent penetration depths are difficult to achieve. Finally, the effects of microstimulation are assessed behaviorally, with no attempt to capture the activity of the local cortical circuits being stimulated. NEW METHOD: We propose a novel method for functional brain mapping, which combines the use of a microelectrode array with intrinsic optical imaging. The precise spacing of electrodes allows for fast, accurate mapping of the area of interest in a regular grid. At the same time, the optical window allows for visualization of local neural connections when stimulation is combined with intrinsic optical imaging. RESULTS: We demonstrate the efficacy of our technique using the primate motor cortex as a sample application, using a combination of microstimulation, imaging and electrophysiological recordings during wakefulness and under anesthesia. Comparison with current method: We find the data collected with our method is consistent with previous data published by others. We believe that our approach enables data to be collected faster and in a

more consistent fashion and makes possible a number of studies that would be difficult to carry out with the traditional approach. CONCLUSIONS: Our technique allows for simultaneous modulation and imaging of cortical sensorimotor networks in wakeful subjects over multiple sessions which is highly desirable for both the study of cortical organization and the design of brain machine interfaces.

Chew, G. M., Fujita, T., Webb, G. M., Burwitz, B. J., Wu, H. L., Reed, J. S., et al. (2016). TIGIT marks exhausted T cells, correlates with disease progression, and serves as a target for immune restoration in HIV and SIV infection. *PLoS Pathogens, 12*(1), e1005349.
HIV infection induces phenotypic and functional changes to CD8+ T cells defined by the coordinated upregulation of a series of negative checkpoint receptors that eventually result in T cell exhaustion and failure to control viral replication. We report that effector CD8+ T cells during HIV infection in blood and SIV infection in lymphoid tissue exhibit higher levels of the negative checkpoint receptor TIGIT. Increased frequencies of TIGIT+ and TIGIT+ PD-1+ CD8+ T cells correlated with parameters of HIV and SIV disease progression. TIGIT remained elevated despite viral suppression in those with either pharmacological antiretroviral control or immunologically in elite controllers. HIV and SIV-specific CD8+ T cells were dysfunctional and expressed high levels of TIGIT and PD-1. Ex-vivo single or combinational antibody blockade of TIGIT and/or PD-L1 restored viral-specific CD8+ T cell effector responses. The frequency of TIGIT+ CD4+ T cells correlated with the CD4+ T cell total HIV DNA. These findings identify TIGIT as a novel marker of dysfunctional HIV-specific T cells and suggest TIGIT along with other checkpoint receptors may be novel curative HIV targets to reverse T cell exhaustion.

Chiang, M. F., Chan, R. V. P., Vinekar, A., & Woo, R. (2016). Science and art in retinopathy of prematurity diagnosis. *Graefe's Archive for Clinical and Experimental Ophthalmology, 254*(1), 201-202.

Chohan, H., Greenfield, A. L., Yadav, V., & Graves, J. (2016). Use of cannabinoids for spasticity and pain management in MS. *Current Treatment Options in Neurology, 18*(1), 1-14.
Several randomized trials have demonstrated potential benefit of cannabis derivatives in the symptomatic treatment of multiple sclerosis (MS) patients. These provide class 1 and 2 evidence

for cannabinoid product use for spasticity and pain in these patients. The precise best ratio or doses are not yet clear. The safety and potential long-term effects of these products on cognitive function in people with MS have not been evaluated. Since short-term memory and processing speed can be significantly impaired in many people with MS, the concern of potential cognitive impairment related to cannabis products needs consideration in clinical care and should be addressed in longer, prospective studies. © 2015, Springer Science+Business Media New York.

Cholerton, B., Larson, E. B., Quinn, J. F., Zabetian, C. P., Mata, I. F., Keene, C. D., et al. (2015). Precision medicine: Clarity for the complexity of dementia. *The American Journal of Pathology,* Three key elements to precision medicine are stratification by risk, detection of pathophysiological processes as early as possible (even before clinical presentation), and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of disease. Used for decades in the management of some rare diseases and now gaining broad currency in cancer care, a precision medicine approach is beginning to be adapted to cognitive impairment and dementia. This review focuses on the application of precision medicine to address the clinical and biological complexity of two common neurodegenerative causes of dementia: Alzheimer disease and Parkinson disease.

Chou, R., Gore, J. L., Buckley, D., Fu, R., Gustafson, K., Griffin, J. C., et al. (2015). Urinary biomarkers for diagnosis of bladder cancer: A systematic review and meta-analysis. *Annals of Internal Medicine, 163*(12), 922-931.
Background: Urinary biomarkers may be a useful alternative or adjunct to cystoscopy for diagnosis of bladder cancer. Purpose: To systematically review the evidence on the accuracy of urinary biomarkers for diagnosis of bladder cancer in adults who have signs or symptoms of the disease or are undergoing surveillance for recurrent disease. Data Sources: Ovid MEDLINE (January 1990 through June 2015), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and reference lists. Study Selection: 57 studies that evaluated the diagnostic accuracy of quantitative or qualitative nuclear matrix protein 22(NMP22), qualitative or quantitative bladder tumor antigen (BTA), fluorescence in situ hybridization (FISH), fluorescent immunohistochemistry (ImmunoCyt [Scimedx]), and Cxbladder (Pacific Edge

Diagnostics USA) using cystoscopy and histopathology as the reference standard met inclusion criteria. Case-control studies were excluded. Data Extraction: Dual extraction and quality assessment of individual studies. Overall strength of evidence (SOE) was also assessed. Data Synthesis: Across biomarkers, sensitivities ranged from 0.57 to 0.82 and specificities ranged from 0.74 to 0.88. Positive likelihood ratios ranged from 2.52 to 5.53, and negative likelihood ratios ranged from 0.21 to 0.48 (moderate SOE for quantitative NMP22, qualitative BTA, FISH, and ImmunoCyt; low SOE for others). For some biomarkers, sensitivity was higher for initial diagnosis of bladder cancer than for diagnosis of recurrence. Sensitivity increased with higher tumor stage or grade. Studies that directly compared the accuracy of quantitative NMP22 and qualitative BTA found no differences in diagnostic accuracy (moderate SOE); head-to-head studies of other biomarkers were limited. Urinary biomarkers plus cytologic evaluation were more sensitive than biomarkers alone but missed about 10% of bladder cancer cases. Limitation: Restricted to English-language studies; no search for studies published only as abstracts; statistical heterogeneity present in most analyses; few studies for qualitative NMP22, quantitative BTA, and Cxbladder; and methodological shortcomings in almost all studies. Conclusion: Urinary biomarkers miss a substantial proportion of patients with bladder cancer and are subject to false-positive results in others. Accuracy is poor for low-stage and low-grade tumors. Primary Funding Source: Agency for Healthcare Research and Quality. (PROSPERO registration number: CRD42014013284) © 2015 American College of Physicians.

Coleman, C. A., Peterson-Perry, S., & Bumsted, T. (2016). Long-term effects of a health literacy curriculum for medical students. *Family Medicine, 48*(1), 49-53.

BACKGROUND AND OBJECTIVES: Although there are reports of short-term benefits of health literacy curricula for improving health care professionals' communication with patients, no studies have included long-term follow-up. We sought to determine (1) whether a pre-clerkship health literacy training can improve medical students' perceived knowledge and intended behaviors vis-a-vis communication with patients who have low health literacy, (2) the longevity of any such impact at 12 months, and (3) the impact of a follow-up training 1 year later. METHODS: We conducted pre-and post-training assessments of selfperceived knowledge and perceived and planned behavior following a health literacy training for first-year medical students, with a 12-

month follow-up training and repeat pre/post assessment. RESULTS: Among 48 pre-clerkship students, improvement was reported on 10 of 12 items following the Year 1 training. At 12-month follow-up, prior to the Year 2 training, ratings on 8 of 10 items had regressed to baseline levels. Nine of these items again improved significantly after the Year 2 training. Students were asked after both trainings if they felt they had overestimated their understanding of health literacy; significantly more students agreed with this statement following the Year 2 training than the Year 1 training. CONCLUSIONS: Among a cohort of pre-clerkship medical students, improvements in perceived knowledge and planned behavior vis-a-vis health literacy training largely did not persist at 12-month follow-up. Efforts to teach medical students about health literacy principles and practices should include a longitudinal or integrated format, rather than a one-time lecture format. and planned behaviors for communicating with patients.7,8 However, no studies have included long-term follow-up, and neurobiological research suggests that long-term retention of knowledge is greatly enhanced with repeated exposure and active engagement of the learner.9 We aimed to determine: (1) whether a pre-clerkship health literacy training can improve medical students' perceived knowledge and intended behaviors vis-à-vis communication with patients who have low health literacy, (2) the longevity of any such impact at 12 months, and (3) the impact of a follow-up training 1 year later.

Condron, M. E., Pommier, S. J., & Pommier, R. F. (2016). Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. *Surgery (United States), 159*(1), 358-365.

Background Operations and anesthesia in carcinoid patients can provoke carcinoid crises, which can have serious sequelae, including death. Prophylactic octreotide is recommended to prevent crises. Recommended prophylaxis regimens vary from octreotide long-acting repeatable to preoperative bolus to continuous octreotide infusion; however, efficacy data are lacking. We have shown previously that crises correlated with major complications and that octreotide long-acting repeatable and preoperative bolus failed to prevent crises. This study examines the impact of continuous octreotide infusion. Methods A total of 127 patients (71% with liver metastases, 74% with carcinoid syndrome) who underwent 150 operations with continuous octreotide infusions

were enrolled in this prospective case series. Our main outcome measures were the occurrence of intraoperative carcinoid crises and post-operative complications. Results Crises occurred at a rate of 30% as compared with 24% in our previous series, which examined the impact of preoperative octreotide bolus. Crises were significantly associated with the presence of hepatic metastases (P =.02) or history of carcinoid syndrome (P =.006), although neither was required for crises. Prompt vasopressor treatment shortened the mean duration of hypotension to 8.7 minutes, compared with 19 minutes in our prior series. Crises no longer correlated with major complications (P =.481) unless instability persisted for greater than 10 minutes (P =.011). Conclusion Octreotide infusions do not prevent intraoperative crises. Patients without liver metastases or carcinoid syndrome can have intraoperative crises. Postoperative complications can be decreased by reducing the duration of crises. Further study is needed to determine how best to shorten hemodynamic instability during crises.

Convissar, S. M., Bennett, J., Baumgarten, S. C., Lydon, J. P., DeMayo, F. J., & Stocco, C. (2015). GATA4 and GATA6 knockdown during luteinization inhibits progesterone production and gonadotropin responsiveness in the corpus luteum of female mice. *Biology of Reproduction, 93*(6) The surge of luteinizing hormone triggers the genomic reprogramming, cell differentiation, and tissue remodeling of the ovulated follicle, leading to the formation of the corpus luteum. During this process, called luteinization, follicular granulosa cells begin expressing a new set of genes that allow the resulting luteal cells to survive in a vastly different hormonal environment and to produce the extremely high amounts of progesterone (P4) needed to sustain pregnancy. To better understand the molecular mechanisms involved in the regulation of luteal P4 production in vivo, the transcription factors GATA4 and GATA6 were knocked down in the corpus luteum by crossing mice carrying Gata4 and Gata6 floxed genes with mice carrying Cre recombinase fused to the progesterone receptor. This receptor is expressed exclusively in granulosa cells after the luteinizing hormone surge, leading to recombination of floxed genes during follicle luteinization. The findings demonstrated that GATA4 and GATA6 are essential for female fertility, whereas targeting either factor alone causes subfertility. When compared to control mice, serum P4 levels and luteal expression of key steroidogenic genes were significantly lower in conditional knockdown mice. The results also showed that GATA4 and GATA6 are required for the expression

of the receptors for prolactin and luteinizing hormone, the main luteotropic hormones in mice. The findings demonstrate that GATA4 and GATA6 are crucial regulators of luteal steroidogenesis and are required for the normal response of luteal cells to luteotropins. ©2015 by the Society for the Study of Reproduction, Inc.

Cook, M. R., Graff-Baker, A. N., Moren, A. M., Brown, S., Fair, K. A., Kiraly, L. N., et al. (2016). A disease-specific hybrid rotation increases opportunities for deliberate practice. *Journal of Surgical Education, 73*(1), 1-6.

Importance Incorporating deliberate practice (DP) into residency curricula may optimize education. DP includes educationally protected time, continuous expert feedback, and a focus on a limited number of technical skills. It is strongly associated with mastery level learning. Objective Determine if a multidisciplinary breast rotation (MDB) increases DP opportunities. Design Beginning in 2010, interns completed the 4-week MDB. Three days a week were spent in surgery and surgical clinic. Half-days were in breast radiology, pathology, medical oncology, and didactics. The MDB was retrospectively compared with a traditional community rotation (TCR) and a university surgical oncology service (USOS) using rotation feedback and resident operative volume. Data are presented as mean ± standard deviation. Setting Oregon Health and Science University in Portland, Oregon; an academic tertiary care general surgery residency program. Participants General surgery residents at Oregon Health and Science University participating in either the MDB, TCR or USOS. Results A total of 31 interns rated the opportunity to perform procedures significantly higher for MDB than TCR or USOS (4.6 ± 0.6 vs 4.2 ± 0.9 and 4.1 ± 1.0, $p < 0.05$). MDB was rated higher than TCR on quality of faculty teaching and educational materials (4.5 ± 0.7 vs 4.1 ± 0.9 and 4.0 ± 1.2 vs 3.5 ± 1.0, $p < 0.05$). Interns operated more on the MDB than on the USOS and were more focused on breast resections, lymph node dissections, and port placements than on the traditional surgical rotation or USOS. Conclusions The MDB incorporates multidisciplinary care into a unique, disease-specific, and educationally focused rotation. It is highly rated and affords a greater opportunity for DP than either the USOS or TCR. DP is strongly associated with mastery learning and this novel rotation structure could maximize intern education in the era of limited work hours. © 2015 Association of Program Directors in Surgery.

Cornelius, R. J., Wang, B., Wang-France, J., & Sansom, S. C. (2016). Maintaining K balance on the low na, high K diet. *American Journal of Physiology.Renal Physiology,* , ajprenal.00330.2015.

A low Na, high K diet (LNaHK) is considered a healthier alternative to the "Western" high Na diet. Because the mechanism for K secretion involves Na reabsorptive exchange for secreted K in the distal nephron, it is not understood how K is eliminated with such low Na intake. Animals on LNaHK produce an alkaline load, high urinary flows, and markedly elevated plasma angiotensin II (ANGII) and aldosterone (aldo) levels in order to maintain K balance. Recent studies have revealed a potential mechanism involving the actions of alkalosis, urinary flow, elevated ANGII, and aldo on two types of potassium channels, ROMK and BK, located in principal and intercalated cells. Here we review these recent advances.

Costantino, C., Thomas, G. V., Ryan, C., Coakley, F. V., & Troxell, M. L. (2016). Metastatic renal cell carcinoma without evidence of a renal primary. *International Urology and Nephrology, 48*(1), 73-77.

Purpose: Metastatic renal cell carcinoma (RCC), without an identified kidney primary, has been reported rarely. We report a patient with RCC metastatic to bilateral adrenal glands and liver, without an apparent renal primary. We detail the immunohistochemical and molecular studies employed to substantiate the diagnosis of RCC and direct therapy. Methods: Histopathologic findings were correlated with imaging data and supplemented by a panel of immunohistochemical stains, as well as tumor sequence analysis. Results: Despite the presence of bilateral adrenal masses and lack of tumor within kidney parenchyma, the diagnosis of RCC was substantiated by immunohistochemistry (RCC+/PAX2+/PAX8+/Melan-A−/SF-1− among others) and molecular genetic analysis, harboring mutations in VHL,TP53, KDM5C, and PBRM1. After debulking surgery, based on the diagnosis of RCC and the molecular profile, the patient was treated with a tyrosine kinase inhibitor (sunitinib), resulting in stablilization of disease. Conclusions: This case illustrates the role of mutational analysis in carcinomas with rare or unusual presentations, such as metastatic RCC without a renal primary.

Crabbe, J. C. (2014). Alcohol-use disorders. (pp. 293-302) Cambridge University Press.

The two most widely used sets of diagnostic criteria for alcoholuse disorders (AUD)-DSM-IV and

ICD-10-replace the older descriptor, "alcoholism, " and distinguish alcohol dependence as a more severe diagnosis from alcohol abuse (Hasin, 2003). Current proposed revisions for DSM-V will abolish this distinction (Hasin, 2012). Symptoms leading to this diagnosis in both systems include tolerance and withdrawal (or drinking to relieve withdrawal). However, most symptoms are deined behaviorally, and include loss of control, neglect of other activities, and continued drinking in the face of clear negative consequences. Persistence of multiple symptoms is required to earn a diagnosis (Hasin, 2003). his etiologic The terogeneity and the consequent The terogeneity of genetic risk means tome that there is no such thing as a "complete" genetic animalmodel for AUD, as it is a diffuse and moving target. Furthermore, there is substantial complexity introduced by the extensive comorbidity of AUD with personality and disease entities such as anxiety, depression, impulsivity, general disinhibition, and externalizing disorders, to name a few. Therefore, genetic animal models are partial, and target specific features of AUD. © Cambridge University Press 2014.

Crawford, D. C., Li, C. S., Sprague, S., & Bhandari, M. (2015). Clinical and cost implications of inpatient versus outpatient orthopedic surgeries: A systematic review of the published literature. *Orthopedic Reviews, 7*(4), 6177.

The number of outpatient orthopedic surgeries performed within North America continues to increase. The impact of this change in services on patient outcomes is largely unknown. The objective of this review is to compare patient outcomes and associated costs for outpatient orthopedic surgeries traditionally performed in hospital to inpatient surgeries, as well as to summarize the eligibility and preoperative education requirements for outpatient orthopedic surgery in North America. We performed a systematic review of Medline, Pubmed and Embase databases for articles comparing the clinical and economic impact of outpatient orthopedic surgical procedures versus inpatient procedures in North America. We reported on requirements for inpatient versus outpatient care, preoperative education requirements, complications and patient outcomes, patient satisfaction, and when available total mean costs. Nine studies met the inclusion criteria for this review. Eligibility requirements for outpatient orthopedic surgery within the included studies varied, but generally included: patient consent, a caregiver at home following surgery, close proximity to an outpatient center, and no history of serious medical

problems. Preoperative education programs were not always compulsory and practices varied between outpatient centers. All of the reviewed studies reported that outpatient surgeries had similar or improved level of pain and rates of nausea. Outpatients reported increased satisfaction with the care they received. As expected, outpatient procedures were less expensive than inpatient procedures. This review found that outpatient procedures in North America appear to be less expensive and safe alternatives to inpatient care for patients who are at lower risk for complications and procedures that do not necessarily require close hospital level care monitoring following same day surgery.

Crawford, J. D., Hsieh, C. M., Schenning, R. C., Slater, M. S., Landry, G. J., Moneta, G. L., et al. (2016). Genetics, pregnancy, and aortic degeneration. *Annals of Vascular Surgery, 30*, 158.e5-158.e9.

We present a case of familial thoracic aortic aneurysm and dissection (FTAAD) in a pregnant female. FTAAD is an inherited, nonsyndromic aortopathy resulting from several genetic mutations critical to aortic wall integrity have been identified. One such mutation is the myosin heavy chain gene (MYH11) which is responsible for 1-2% of all FTAAD cases. This mutation results in aortic medial degeneration, loss of elastin, and reticulin fiber fragmentation predisposing to TAAD. Aortic disease is more aggressive during pregnancy as a result of increased wall stress from hyperdynamic cardiovascular changes and estrogen-induced aortic media degeneration. Our patient was a 29-year-old G2P1 woman at 26 weeks gestation presenting with abdominal and back pain. Work-up revealed a 6.4-cm ascending aortic aneurysm with a type A dissection extending into all arch vessels, aortic coarctation at the isthmus, and a separate focal type B aortic dissection with visceral involvement. Surgical management included concomitant cesarean section with delivery of a live premature infant, tubal ligation, ascending aortic replacement with reconstruction of the arch vessels, and aortic valve resuspension. The type B dissection was managed medically without complication. This is the first reported case of aortic dissection in a patient with FTAAD/MYH11 mutation and pregnancy. This case highlights that FTAAD and pregnancy cause aortic degeneration via distinct mechanisms and that hyperdynamics of pregnancy increase aortic wall stress. Management of pregnancy associated with aortopathy

requires early transfer to a tertiary center, careful investigation to identify familial aortopathy, fetal monitoring, and a multidisciplinary team approach.

Cservenka, A., & Nagel, B. J. (2016). Neuroscience of alcohol for addiction medicine: Neurobiological targets for prevention and intervention in adolescents. *Progress in Brain Research, 223*, 215-235.
Structural and functional neuroimaging studies indicate that heavy alcohol use during adolescence may be neurotoxic to the brain. This chapter reviews the neuroimaging findings in cross-sectional and longitudinal studies of adolescent heavy alcohol users. These youth exhibit reductions in prefrontal, hippocampal, and cerebellar brain volume, decreased frontoparietal, and increased frontolimbic white matter integrity, as well as alterations in blood oxygen level-dependent response during working memory, inhibitory control, verbal encoding, decision making, and reward processing-some of which appear to differ between males and females. Although some exist, additional longitudinal studies will significantly advance addiction medicine by aiding prevention scientists and treatment providers to develop neurobiologically informed ways of strengthening neural networks prior to and after the onset of heavy alcohol use, thereby promoting healthy cognitive functioning across the adolescent period.

Cuevas-Ramos, D., & Fleseriu, M. (2016). Pasireotide: A novel treatment for patients with acromegaly. *Drug Design, Development and Therapy, 10*, 227-239.
Morbidity and mortality rates in patients with active acromegaly are higher than the general population. Adequate biochemical control restores mortality to normal rates. Now, medical therapy has an increasingly important role in the treatment of patients with acromegaly. Somatostatin receptor ligands (SRLs) are considered the standard medical therapy, either after surgery or as a first-line therapy when surgery is deemed ineffective or is contraindicated. Overall, octreotide and lanreotide are first-generation SRLs and are effective in ~20%-70% of patients. Pegvisomant, a growth hormone receptor antagonist, controls insulin-like growth factor 1 in 65%-90% of cases. Consequently, a subset of patients (nonresponders) requires other treatment options. Drug combination therapy offers the potential for more efficacious disease control. However, the development of new medical therapies remains essential. Here, emphasis is placed on new medical therapies to control acromegaly. There is a focus on pasireotide long-

acting release (LAR) (Signifor LAR((R))), which was approved in 2014 by the US Food and Drug Administration and the European Medicine Agency for the treatment of acromegaly. Pasireotide LAR is a long-acting somatostatin multireceptor ligand. In a Phase III clinical trial in patients with acromegaly (naive to medical therapy or uncontrolled on a maximum dose of first-generation SRLs), 40 and 60 mg of intramuscular pasireotide LAR achieved better biochemical disease control than octreotide LAR, and tumor shrinkage was noted in both pasireotide groups. Pasireotide LAR tolerability was similar to other SRLs, except for a greater frequency and degree of hyperglycemia and diabetes mellitus. Baseline glucose may predict hyperglycemia occurrence after treatment, and careful monitoring of glycemic status and appropriate treatment is required. A precise definition of patients with acromegaly who will derive the greatest therapeutic benefit from pasireotide LAR remains to be established. Lastly, novel therapies and new potential delivery modalities (oral octreotide) are summarized.

Daneshgari, F., Paspulati, R. M., & Simon, J. H. (2014). Bladder, bowel, and sexual dysfunction. (pp. 260-269) Cambridge University Press.

The main focus of this chapter is neurogenic bladder dysfunction, mostly referred to as neurogenic bladder (NGB), which is a dysfunction of the urinary bladder due to diseases of the central and/or peripheral nervous system that control bladder function [1]. The acute neurological disorders affecting bowel (e.g. neurogenic bowel) and sexual function (e.g. erectile dysfunction) are briefly considered within the context of associated dysfunctions as there are common and overlapping neurological pathways and pathologies affecting the three functional systems. Common diseases of the nervous system that affect the bladder, bowel, and sexual function include multiple sclerosis (MS), spinal cord injury, spina bifida, and other congenital anomalies, Parkinson’s disease, cerebrovascular events/stroke, and localized infectious/inflammatory disease affecting the spinal cord and nerve roots [2-5]. For MS alone, according to recent estimates, there are approximately 350 000 people in the USA with physician-diagnosed disease and worldwide estimates are on the order of 2.5 million people. The prevalence of NGB is more than 96% in patients with MS with duration longer than 10 years [2]. Long-term bladder, as well as bowel and sexual dysfunction contribute markedly to the morbidity

and are major quality-of-life issues after spinal trauma, which also strikes individuals early in their lives. © Cambridge University Press 2014.

Daniels, A. H., Smith, J. S., Hiratzka, J., Ames, C. P., Bess, S., Shaffrey, C. I., et al. (2015). Functional limitations due to lumbar stiffness in adults with and without spinal deformity. *Spine, 40*(20), 1599-1604.

STUDY DESIGN: Cross-sectional analysis. OBJECTIVE: To compare Lumbar Stiffness Disability Index (LSDI) scores between asymptomatic adults and patients with spinal deformity. SUMMARY OF BACKGROUND DATA: The LSDI was designed and validated as a tool to assess functional impacts of lumbar spine stiffness and diminished spinal flexibility. Baseline disability levels of patients with adult spinal deformity (ASD) are high as measured by multiple validated outcome tools. Baseline lumbar stiffness-related disability has not been assessed in adults with and without spinal deformity. METHODS: The LSDI and Scoliosis Research Society-22r (SRS-22r) were submitted to a group of asymptomatic adult volunteers. Additionally, a multicenter cross-sectional cohort analysis of patients with ASD from 10 centers was conducted. Baseline LSDI and SRS-22r were completed for both operatively and nonoperatively treated patients with deformity. RESULTS: The LSDI was completed by 176 asymptomatic volunteers and 693 patients with ASD. Mean LSDI score for asymptomatic volunteers was 3.4 +/- 6.3 out of a maximum score of 100, with significant correlation between increasing age and higher (worse) LSDI score ($r = 0.30$, $P = 0.0001$). Of the patients with spinal deformity undergoing analysis, 301 subsequently underwent surgery and 392 were subsequently treated nonoperatively. Operative patients had significantly higher preoperative LSDI scores than both nonoperative patients and asymptomatic volunteers (29.9 vs. 17.3 vs. 3.4, $P < 0.0001$ for both). For patients with ASD, significant correlations were found between LSDI and SRS-22 Pain and Function subscales ($r = -0.75$ and -0.76, respectively; $P < 0.0001$ for both). CONCLUSION: LSDI scores are low among asymptomatic volunteers, although stiffness-related disability increases with increasing age. Patients with ASD report substantial stiffness-related disability even prior to surgical fusion. Stiffness-related disability correlates with pain- and function-related disability measures among patients with spinal deformity. LEVEL OF EVIDENCE: 1.

Darnall, B. D., Scheman, J., Davin, S., Burns, J. W., Murphy, J. L., Wilson, A. C., et al. (2016). Pain psychology: A global needs assessment and national call to action. *Pain Medicine (Malden, Mass.),*

OBJECTIVE: The Institute of Medicine and the draft National Pain Strategy recently called for better training for health care clinicians. This was the first high-level needs assessment for pain psychology services and resources in the United States. DESIGN: Prospective, observational, cross-sectional. METHODS: Brief surveys were administered online to six stakeholder groups (psychologists/therapists, individuals with chronic pain, pain physicians, primary care physicians/physician assistants, nurse practitioners, and the directors of graduate and postgraduate psychology training programs). RESULTS: 1,991 responses were received. Results revealed low confidence and low perceived competency to address physical pain among psychologists/therapists, and high levels of interest and need for pain education. We found broad support for pain psychology across stakeholder groups, and global support for a national initiative to increase pain training and competency in U.S. therapists. Among directors of graduate and postgraduate psychology training programs, we found unanimous interest for a no-cost pain psychology curriculum that could be integrated into existing programs. Primary barriers to pain psychology include lack of a system to identify qualified therapists, paucity of therapists with pain training, limited awareness of the psychological treatment modality, and poor insurance coverage. CONCLUSIONS: This report calls for transformation within psychology predoctoral and postdoctoral education and training and psychology continuing education to include and emphasize pain and pain management. A system for certification is needed to facilitate quality control and appropriate reimbursement. There is a need for systems to facilitate identification and access to practicing psychologists and therapists skilled in the treatment of pain.

Daughtry, B. L., & Chavez, S. L. (2016). Chromosomal instability in mammalian pre-implantation embryos: Potential causes, detection methods, and clinical consequences. *Cell and Tissue Research, 363*(1), 201-225.

Formation of a totipotent blastocyst capable of implantation is one of the first major milestones in early mammalian embryogenesis, but less than half of in vitro fertilized embryos from most mammals will progress to this stage of development. Whole chromosomal abnormalities, or

aneuploidy, are key determinants of whether human embryos will arrest or reach the blastocyst stage. Depending on the type of chromosomal abnormality, however, certain embryos still form blastocysts and may be morphologically indistinguishable from chromosomally normal embryos. Despite the implementation of pre-implantation genetic screening and other advanced in vitro fertilization (IVF) techniques, the identification of aneuploid embryos remains complicated by high rates of mosaicism, atypical cell division, cellular fragmentation, sub-chromosomal instability, and micro-/multi-nucleation. Moreover, several of these processes occur in vivo following natural human conception, suggesting that they are not simply a consequence of culture conditions. Recent technological achievements in genetic, epigenetic, chromosomal, and non-invasive imaging have provided additional embryo assessment approaches, particularly at the single-cell level, and clinical trials investigating their efficacy are continuing to emerge. In this review, we summarize the potential mechanisms by which aneuploidy may arise, the various detection methods, and the technical advances (such as time-lapse imaging, "-omic" profiling, and next-generation sequencing) that have assisted in obtaining this data. We also discuss the possibility of aneuploidy resolution in embryos via various corrective mechanisms, including multi-polar divisions, fragment resorption, endoreduplication, and blastomere exclusion, and conclude by examining the potential implications of these findings for IVF success and human fecundity.

de Melo Campos, P., Machado-Neto, J. A., Eide, C. A., Savage, S. L., Scopim-Ribeiro, R., Duarte, A. D., et al. (2016). IRS2 silencing increases apoptosis and potentiates the effects of ruxolitinib in JAK2V617F-positive myeloproliferative neoplasms. *Oncotarget,*

The recurrent V617F mutation in JAK2 (JAK2V617F) has emerged as the primary contributor to the pathogenesis of myeloproliferative neoplasms (MPN). However, the lack of complete response in most patients treated with the JAK1/2 inhibitor, ruxolitinib, indicates the need for identifying pathways that cooperate with JAK2. Activated JAK2 was found to be associated with the insulin receptor substrate 2 (IRS2) in non-hematological cells. We identified JAK2/IRS2 binding in JAK2V617F HEL cells, but not in the JAK2WT U937 cell line. In HEL cells, IRS2 silencing decreased STAT5 phosphorylation, reduced cell viability and increased apoptosis; these effects were enhanced when IRS2 silencing was combined with ruxolitinib. In U937 cells, IRS2 silencing

neither reduced cell viability nor induced apoptosis. IRS1/2 pharmacological inhibition in primary MPN samples reduced cell viability in JAK2V617F-positive but not JAK2WT specimens; combination with ruxolitinib had additive effects. IRS2 expression was significantly higher in CD34+ cells from essential thrombocythemia patients compared to healthy donors, and in JAK2V617F MPN patients when compared to JAK2WT. Our data indicate that IRS2 is a binding partner of JAK2V617F in MPN. IRS2 contributes to increased cell viability and reduced apoptosis in JAK2-mutated cells. Combined pharmacological inhibition of IRS2 and JAK2 may have a potential clinical application in MPN.

Denneson, L. M., Williams, H. B., Kaplan, M. S., McFarland, B. H., & Dobscha, S. K. (2016). Treatment of veterans with mental health symptoms in VA primary care prior to suicide. *General Hospital Psychiatry, 38*, 65-70.

Objective: We describe Veterans Affairs (VA) primary care received by veterans with mental health symptoms in the year prior to suicide to identify opportunities to improve care. Method: Death certificate data from 11 states were linked to VA national patient care data for veterans who died by suicide in 2009 and had received VA care. We identified 118 age-, sex- and clinician-matched case-control pairs (suicide decedents and living controls) with mental health symptoms. Using McNemar's chi-square and paired t tests, we compare primary care follow-up received during the year prior to death. Results: Cases and controls received similar primary care clinician follow-up and treatment for mental health symptoms. Cases were less likely than controls to fill 90 or more total days of an antidepressant during the year (P = .02), despite no differences in prescription orders from clinicians (P = .05). Cases and controls were equally likely to fill 90 or more consecutive days of an antidepressant (P = .47). Across both groups, 48% (n = 113) received assessment for suicidal ideation in primary care. Conclusion: We identified two areas to improve primary care for veterans at risk for suicide: monitoring antidepressant treatment adherence and improving suicidal ideation assessment and follow-up for veterans with mental health symptoms. © 2015.

Deodhar, A., Mease, P. J., Reveille, J. D., Curtis, J. R., Chen, S., Malhotra, K., et al. (2016). Frequency of axial spondyloarthritis diagnosis among patients seen by united states rheumatologists for

evaluation of chronic back pain. *Arthritis & Rheumatology (Hoboken, N.J.),*

Objective To determine the proportion of patients with axial spondyloarthritis (axSpA) among those with chronic back pain and >/=1 of 3 SpA features in the United States (US). Methods The study was conducted at rheumatology practices in the US. Patients were required to have chronic back pain for >/=3 months beginning at /=1 of 3 SpA features: 1) positive human leukocyte antigen B27 (HLA-B27), 2) current inflammatory back pain, 3) MRI/x-ray evidence of sacroiliitis, and no prior SpA diagnosis. Medical history/physical exam, pelvic x-ray, MRI of sacroiliac joints, CRP, and HLA-B27 were collected. Investigators were asked if a clinical diagnosis of axSpA could be made based upon results. Data were also analyzed separately to determine if patients fulfilled Assessment of SpondyloArthritis international Society (ASAS) criteria for axSpA and/or modified New York criteria for ankylosing spondylitis (AS). Results 751 patients were enrolled (46% existing patients in rheumatology practices, 40% new referrals, 14% self-referred). Among patients with available data, 319/697 (46%) were given a clinical diagnosis of axSpA by the investigator; 348/744 (47%) fulfilled ASAS criteria, of whom 238 were classified as non-radiographic axSpA, 108 as AS, and 2 had missing data. Using investigator's clinical diagnosis as the gold standard, specificity and sensitivity of the ASAS criteria were 79% and 81%, respectively. Conclusion Among patients with chronic back pain for >/=3 months beginning at age /=1 of 3 SpA features is an effective way to identify patients with possible axSpA. This article is protected by copyright. All rights reserved.

Deyo, R. A., Ramsey, K., Buckley, D. I., Michaels, L., Kobus, A., Eckstrom, E., et al. (2015). Performance of a patient reported outcomes measurement information system (PROMIS) short form in older adults with chronic musculoskeletal pain. *Pain Medicine (Malden, Mass.),*

OBJECTIVE: . To assess reliability, validity, and responsiveness of a 29-item short-form version of the Patient Reported Outcomes Measurement Information System (PROMIS) and a novel "impact score" calculated from those measures. DESIGN: . Prospective cohort study. SETTING: . Rural primary care practices. SUBJECTS: . Adults aged >/= 55 years with chronic musculoskeletal pain, not currently receiving prescription opioids. METHODS: . Subjects completed the PROMIS short form at baseline and after 3 months. Patient subsets were compared to assess reliability and responsiveness. Construct validity was tested by comparing baseline scores among patients who

were or were not applying for Worker's Compensation; those with higher or lower catastrophizing scores; and those with or without recent falls. Responsiveness was assessed with mean score changes, effect sizes, and standardized response means. RESULTS: . Internal consistency was good to excellent, with Cronbach's alpha between 0.81 and 0.95 for all scales. Among patients who rated their pain as stable, test-retest scores at 3 months were around 0.70 for most scales. PROMIS scores were worse among patients seeking or receiving worker's compensation, those with high catastrophizing scores, and those with recent falls. Among patients rating pain as "much less" at 3 months, absolute effect sizes for the various scales ranged from 0.24 (Depression) to 1.93 (Pain Intensity). CONCLUSIONS: . Results indicate that the PROMIS short 29-item form may be useful for the study of patients with chronic musculoskeletal pain. Our findings also support use of the novel "impact score" recommended by the National Institutes of Health (NIH) Task Force on Research Standards for Chronic Low Back Pain.

Didier, R. A., Vajtai, P. L., & Hopkins, K. L. (2015). Iterative reconstruction technique with reduced volume CT dose index: Diagnostic accuracy in pediatric acute appendicitis. *Pediatric Radiology, 45*(2), 181-187.

BACKGROUND: Iterative reconstruction technique has been proposed as a means of reducing patient radiation dose in pediatric CT. Yet, the effect of such reductions on diagnostic accuracy has not been thoroughly evaluated. OBJECTIVE: This study compares accuracy of diagnosing pediatric acute appendicitis using contrast-enhanced abdominopelvic CT scans performed with traditional pediatric weight-based protocols and filtered back projection reconstruction vs. a filtered back projection/iterative reconstruction technique blend with reduced volume CT dose index (CTDIvol). MATERIALS AND METHODS: Results of pediatric contrast-enhanced abdominopelvic CT scans done for pain and/or suspected appendicitis were reviewed in two groups: A, 192 scans performed with the hospital's established weight-based CT protocols and filtered back projection reconstruction; B, 194 scans performed with iterative reconstruction technique and reduced CTDIvol. Reduced CTDIvol was achieved primarily by reductions in effective tube current-time product (mAseff) and tube peak kilovoltage (kVp). CT interpretation was correlated with clinical follow-up and/or surgical pathology. CTDIvol, size-specific dose estimates (SSDE) and performance characteristics of the two CT techniques were then compared.

RESULTS: Between groups A and B, mean CTDIvol was reduced by 45%, and mean SSDE was reduced by 46%. Sensitivity, specificity and diagnostic accuracy were 96%, 97% and 96% in group A vs. 100%, 99% and 99% in group B. CONCLUSION: Accuracy in diagnosing pediatric acute appendicitis was maintained in contrast-enhanced abdominopelvic CT scans that incorporated iterative reconstruction technique, despite reductions in mean CTDIvol and SSDE by nearly half as compared to the hospital's traditional weight-based protocols.

Dixit, S., Stein, P. K., Dewland, T. A., Dukes, J. W., Vittinghoff, E., Heckbert, S. R., et al. (2016). Consumption of caffeinated products and cardiac ectopy. *Journal of the American Heart Association, 5*(1), 10.1161/JAHA.115.002503.

BACKGROUND: Premature cardiac contractions are associated with increased morbidity and mortality. Though experts associate premature atrial contractions (PACs) and premature ventricular contractions (PVCs) with caffeine, there are no data to support this relationship in the general population. As certain caffeinated products may have cardiovascular benefits, recommendations against them may be detrimental. METHODS AND RESULTS: We studied Cardiovascular Health Study participants with a baseline food frequency assessment, 24-hour ambulatory electrocardiography (Holter) monitoring, and without persistent atrial fibrillation. Frequencies of habitual coffee, tea, and chocolate consumption were assessed using a picture-sort food frequency survey. The main outcomes were PACs/h and PVCs/hour. Among 1388 participants (46% male, mean age 72 years), 840 (61%) consumed >/=1 caffeinated product per day. The median numbers of PACs and PVCs/h and interquartile ranges were 3 (1-12) and 1 (0-7), respectively. There were no differences in the number of PACs or PVCs/h across levels of coffee, tea, and chocolate consumption. After adjustment for potential confounders, more frequent consumption of these products was not associated with ectopy. In examining combined dietary intake of coffee, tea, and chocolate as a continuous measure, no relationships were observed after multivariable adjustment: 0.48% fewer PACs/h (95% CI -4.60 to 3.64) and 2.87% fewer PVCs/h (95% CI -8.18 to 2.43) per 1-serving/week increase in consumption. CONCLUSIONS: In the largest study to evaluate dietary patterns and quantify cardiac ectopy using 24-hour Holter monitoring, we found no relationship between chronic consumption of caffeinated products and ectopy.

Dobscha, S. K., Denneson, L. M., Jacobson, L. E., Williams, H. B., Cromer, R., & Woods, S. (2016). VA mental health clinician experiences and attitudes toward OpenNotes. *General Hospital Psychiatry, 38*, 89-93.

Objective: To describe Department of Veterans Affairs (VA) mental health clinician attitudes toward and experiences with OpenNotes (also known as Blue Button), which provides patients direct access to clinical notes online. Method: A 35-item online survey was administered to 263 mental health clinicians and nurses from one VA Medical Center. Results: Seventy-nine percent of eligible subjects participated. Most respondents agreed or somewhat agreed that OpenNotes is a good idea in general, but only half agreed that making mental health notes available online is a good idea. Most believed that patients will better remember plans of care and be better prepared for visits. Most also felt that patients will worry more and request changes in notes. Many clinicians reported being less detailed and changing the tone of their notes. Conclusion: As a group, mental health clinicians are positive about OpenNotes in general but ambivalent about the use of OpenNotes in mental health care. The results call for research on outcomes of OpenNotes use in mental health and to develop education and support to help clinicians adapt to OpenNotes.

Drerup, C. M., & Nechiporuk, A. V. (2016). In vivo analysis of axonal transport in zebrafish. *Methods in Cell Biology, 131*, 311-329.

Intracellular transport of proteins and organelles in neurons plays an essential role in nervous system development and maintenance. Axon outgrowth, synapse formation, and synapse function, among other physiological processes, require active transport of these cargos between the neuronal soma and axon terminals. Abnormalities in this axonal transport are associated with a number of neurodevelopmental and neurodegenerative disorders, such as Charcot-Marie-Tooth disease, Alzheimer disease, and amyotrophic lateral sclerosis. Despite its importance for nervous system development and health, methods for visualizing axonal transport in an intact vertebrate have been lacking. Using the advantages of the zebrafish system, we have developed a straightforward approach to visualize axonal transport of various cargos and motor proteins in intact zebrafish embryos and larvae. Here, we describe this approach in detail and discuss how it

can be applied to address questions related to cargo-specific transport regulation and its effects on axon morphology and function in the developing and mature nervous system.

Dudy, S., Asgari, M., & Kain, A. (2015). Pronunciation analysis for children with speech sound disorders. *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2015, , 2015-November.* pp. 5573-5576.

Phonological disorders affect 10% of preschool and school-age children, adversely affecting their communication, academic performance, and interaction level. Effective pronunciation training requires prolonged supervised practice and interaction. Unfortunately, many children do not have access or only limited access to a speech-language pathologist. Computer-assisted pronunciation training has the potential for being a highly effective teaching aid; however, to-date such systems remain incapable of identifying pronunciation errors with sufficient accuracy. In this paper, we propose to improve accuracy by (1) learning acoustic models from a large children's speech database, (2) using an explicit model of typical pronunciation errors of children in the target age range, and (3) explicit modeling of the acoustics of distorted phonemes. © 2015 IEEE.

Dugi, D. D., Simhan, J., & Morey, A. F. (2015). Urethroplasty for stricture disease: Contemporary techniques and outcomes. *Urology,*

Urethral reconstruction is now considered optimal therapy for most men presenting with symptomatic urethral strictures. The rapid development of innovative tissue transfer techniques over the past decade provides today's reconstructive urologist with a high probability of achieving excellent long-term outcomes after urethroplasty, even in the reoperative setting. Fundamental principles such as accurate initial stricture staging by urethrography, along with critical assessment of both stricture severity and tissue quality during urethroplasty are critical for success. This review illustrates the way in which stricture length, location, severity, and etiology influences the application of reconstructive techniques during contemporary urethroplasty.

Eiring, A. M., Khorashad, J. S., Anderson, D. J., Yu, F., Redwine, H. M., Mason, C. C., et al. (2015). β-Catenin is required for intrinsic but not extrinsic BCR-ABL1 kinase-independent resistance to tyrosine kinase inhibitors in chronic myeloid leukemia. *Leukemia, 29*(12), 2328-2337.

Activation of nuclear β-catenin and expression of its transcriptional targets promotes chronic

myeloid leukemia (CML) progression, tyrosine kinase inhibitor (TKI) resistance, and leukemic stem cell self-renewal. We report that nuclear β-catenin has a role in leukemia cell-intrinsic but not -extrinsic BCR-ABL1 kinase-independent TKI resistance. Upon imatinib inhibition of BCR-ABL1 kinase activity, β-catenin expression was maintained in intrinsically resistant cells grown in suspension culture and sensitive cells cultured in direct contact (DC) with bone marrow (BM) stromal cells. Thus, TKI resistance uncouples β-catenin expression from BCR-ABL1 kinase activity. In β-catenin reporter assays, intrinsically resistant cells showed increased transcriptional activity versus parental TKI-sensitive controls, and this was associated with restored expression of β-catenin target genes. In contrast, DC with BM stromal cells promoted TKI resistance, but had little effects on Lef/Tcf reporter activity and no consistent effects on cytoplasmic β-catenin levels, arguing against a role for β-catenin in extrinsic TKI resistance. N-cadherin or H-cadherin blocking antibodies abrogated DC-based resistance despite increasing Lef/Tcf reporter activity, suggesting that factors other than β-catenin contribute to extrinsic, BM-derived TKI resistance. Our data indicate that, while nuclear β-catenin enhances survival of intrinsically TKI-resistant CML progenitors, it is not required for extrinsic resistance mediated by the BM microenvironment. © 2015 Macmillan Publishers Limited.

Elliot, D., Garg, B., Kuehl, K., DeFrancesco, C., & Sleigh, A. (2015). Why are women law enforcement officers more burned-out and what might help them? *Occupational Medicine & Health Affairs, 3*(3), 204. Epub 2015 Jun 11.

Engeland, C. G., Hugo, F. N., Hilgert, J. B., Nascimento, G. G., Junges, R., Lim, H. -., et al. (2016). Psychological distress and salivary secretory immunity. *Brain, Behavior, and Immunity, 52*, 11-17.

Stress-induced impairments of mucosal immunity may increase susceptibility to infectious diseases. The present study investigated the association of perceived stress, depressive symptoms, and loneliness with salivary levels of secretory immunoglobulin A (S-IgA), the subclasses S-IgA1, S-IgA2, and their transporter molecule Secretory Component (SC). S-IgA/SC, IgA1/SC and IgA2/SC ratios were calculated to assess the differential effects of stress on immunoglobulin transport versus availability.This study involved 113 university students, in part

selected on high scores on the UCLA Loneliness Scale and/or the Beck Depression Inventory. Stress levels were assessed using the Perceived Stress Scale. Unstimulated saliva was collected and analysed for total S-IgA and its subclasses, as well as SC and total salivary protein. Multiple linear regression analyses, adjusted for gender, age, health behaviours, and concentration effects (total protein) revealed that higher perceived stress was associated with lower levels of IgA1 but not IgA2. Perceived stress, loneliness and depressive symptoms were all associated with lower IgA1/SC ratios. Surprisingly, higher SC levels were associated with loneliness and depressive symptoms, indicative of enhanced transport activity, which explained a lower IgA1/SC ratio (loneliness and depression) and IgA2/SC ratio (depression).This is the first study to investigate the effects of protracted psychological stress across S-IgA subclasses and its transporter SC. Psychological stress was negatively associated with secretory immunity, specifically IgA1. The lower immunoglobulin/transporter ratio that was associated with higher loneliness and depression suggested a relative immunoglobulin depletion, whereby availability was not keeping up with enhanced transport demand.

Farashishiko, A., Chacón, K. N., Blackburn, N. J., & Woods, M. (2016). Nano assembly and encapsulation; a versatile platform for slowing the rotation of polyanionic Gd3+-based MRI contrast agents. *Contrast Media and Molecular Imaging,*

Encapsulating discrete Gd3+ chelates in nano-assembled capsules (NACs) is a simple and effective method of preparing an MRI contrast agent capable of delivering a large payload of high relaxivity imaging agent. The preparation of contrast agent containing NACs had previously focussed on preparations incorporating GdDOTP5- into the internal aggregate. In this report we demonstrate that other Gd3+ chelates bearing overall charges as low as 2- can also be used to prepare NACs. This discovery opens up the possibility of using Gd3+ chelates that have inner-sphere water molecules that could further increase the relaxivity enhancement associated with the long τR that arises from encapsulation. However, encapsulation of the q=1 chelate GdDTPA2- did not give rise to a significant increase in relaxivity relative to encapsulation of the outer-sphere chelate GdTTHA3-. This leads us to the conclusion that in the NAC interior proton transport is not mediated by movement of whole water molecules and the enhanced relaxivity of Gd3+ chelate

encapsulated within NACs arises primarily from second sphere effects. © 2015 John Wiley & Sons, Ltd.

Felder, K. K., Marshall, L. M., Vaz, L. E., & Barnes, P. D. (2016). Risk factors for complications during outpatient parenteral antimicrobial therapy for adult orthopedic and neurosurgical infections. *Southern Medical Journal, 109*(1), 53-60.

OBJECTIVES: Outpatient parenteral antimicrobial therapy (OPAT) is an effective way of treating infections, but complications are common. We identified patient characteristics and OPAT treatment factors associated with increased risk of OPAT-related complications. METHODS: We used a retrospective cohort design that assessed 337 adult patients treated with OPAT for orthopedic and neurosurgical infections between August 1, 2008 and May 30, 2010. Independent variables included demographics, infection characteristics, lead time factors, OPAT treatment factors, and comorbid conditions. Multivariable log-binomial regression was used to estimate the risk of OPAT complications. RESULTS: The mean patient age was 55 years (range 19-87), 86% had an orthopedic infection, and 44% were treated with intravenous vancomycin. OPAT complications were seen in 45% (152/337) of the cohort. Risk ratios for OPAT complications were 1.9 (95% confidence interval 1.4-2.5) in patients having no primary care provider, 1.7 (95% confidence interval 1.3-2.1) for those treated with vancomycin. CONCLUSIONS: Identifying specific patient characteristics and OPAT treatment factors could facilitate OPAT process improvements to reduce the risk of OPAT complications for vulnerable patients.

Feldstein Ewing, S. W., Apodaca, T. R., & Gaume, J. (2016). Ambivalence: Prerequisite for success in motivational interviewing with adolescents? *Addiction (Abingdon, England),*

BACKGROUND AND AIMS: The exploration and resolution of ambivalence play an essential role in motivational interviewing (MI) theory. However, most adolescent MI studies have not examined ambivalence as a contributor to behaviour change. This paper reviewed research findings on the role of ambivalence in the adolescent change process. METHODS AND RESULTS: We undertook a narrative review of the published empirical and theoretical literature on ambivalence and mechanisms of change in MI for adolescents and found that current MI evaluations appear not to have access to reliable and valid measures of ambivalence in adolescence or neuroimaging

methods to evaluate the mechanisms of treatment response. CONCLUSIONS: Improved instrumentation is needed to assess adolescents' ambivalence in clinical and research settings. Innovative methodology, including neuroimaging, may help identify factors mediating relationships between adolescents' ambivalence and treatment response.

Feldstein Ewing, S. W., Tapert, S. F., & Molina, B. S. (2015). Uniting adolescent neuroimaging and treatment research: Recommendations in pursuit of improved integration. *Neuroscience and Biobehavioral Reviews,*

Many clinicians who provide mental health treatment find developmental neuroscience discoveries to be exciting. However, the utility of these findings often seem far removed from everyday clinical care. Thus, the goal of this article is to offer a bridge to connect the fields of applied adolescent treatment and developmental neuroscience investigation. An overview of the relevance of developmental neuroscience in adolescent direct practice and a rationale for how and why this integration could benefit adolescent treatment outcomes is provided. Finally, a series of practical suggestions is generated for enhancing collaborative, interdisciplinary work that ultimately advances treatment response for this important clinical population.

Filippi, M., & Simon, J. (2014). Preface. *Imaging Acute Neurologic Disease: A Symptom-Based Approach,* , ix-x.

Acute neurologic diseases encompass a wide spectrum of medical illnesses with neurological manifestations which require rapid clinical, paraclinical, and laboratory evaluation as patients are assessed in the emergency department or acute care clinics. In the last decade, imaging has assumed far greater importance in the initial assessment of these patients, and is responsible for much of the cost and resources in the early, critical evaluation. However, the optimal approach to utilization of imaging for thorough, yet efficient and cost-responsible, care remains poorly defined for many acute neurologic presentations. Many radiologic texts provide an invaluable overview of the many important details of the pathology of neurologic disease. But patients present to the emergency room or clinic with symptoms which typically are thoughtfully considered and guide the clinician through a decision-making process that ultimately determines the type, order, and priorities for further testing, including imaging when indicated. We have therefore prioritized a

symptom-based approach to imaging in acute neurologic disease, based on the practice parameters developed by experts in the field, combining expert clinicians and imagers for each chapter. The task of developing symptom-based imaging algorithms is not always straightforward, and it is recognized that there are many potential variations in approach that are equally valid. The reader will observe that each team of authors has developed a personalized approach to the question based on their practice pattern and expertise. The approaches described in each chapter should provide a framework that we hope can be utilized by the reader to refine their approach, suggest alternative pathways, or encourage and stimulate discussion in the clinical and imaging circles that can ultimately result in more optimal clinical care. © Cambridge University Press 2014.

Filippi, M., & Simon, J. H. (2014). Imaging acute neurologic disease: A symptom-based approach. (pp. 1-382) Cambridge University Press.

While conventional magnetic resonance, X-ray-based, ultrasound, and nuclear medicine techniques are widely used to facilitate diagnosis, inform therapeutic decision-making, provide information regarding prognosis, and monitor therapeutic response in neurologic diseases, their practical value in acute clinical care is not as yet well-defined and the potential future development is not fully appreciated. This book provides a comprehensive survey of best practice for specialists and trainees in neurology, emergency medicine, neuroradiology, radiology, neurosurgery, and critical care. The symptom-based approach guides the choice of the available imaging tools for efficient, accurate, and cost-effective diagnosis to support immediate management of common and complex neurological disorders in the acute setting. Effective examination algorithms are included that integrate neurological and imaging concepts with the practical demands and constraints of emergency care. Written by leading international authorities, the book is extensively illustrated and contains many helpful case-histories. © Cambridge University Press 2014.

Fink, H. A., Litwack-Harrison, S., Taylor, B. C., Bauer, D. C., Orwoll, E. S., Lee, C. G., et al. (2016). Clinical utility of routine laboratory testing to identify possible secondary causes in older men with osteoporosis: The osteoporotic fractures in men (MrOS) study. *Osteoporosis International, 27*(1),

331-338.

Summary: We investigated the value of routine laboratory testing for identifying underlying causes in older men diagnosed with osteoporosis. Most osteoporotic and nonosteoporotic men had ≥1 laboratory abnormality. Few individual laboratory abnormalities were more common in osteoporotic men. The benefit of routine laboratory testing in older osteoporotic men may be low.

Introduction: To evaluate the utility of recommended laboratory testing to identify secondary causes in older men with osteoporosis, we examined prevalence of laboratory abnormalities in older men with and without osteoporosis. Methods: One thousand five hundred seventy-two men aged ≥65 years in the Osteoporotic Fractures in Men study completed bone mineral density (BMD) testing and a battery of laboratory measures, including serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), 25-OH vitamin D, total testosterone, spot urine calcium/creatinine ratio, spot urine albumin/creatinine ratio, creatinine-derived estimated glomerular filtration rate, 24-h urine calcium, and 24-h urine free cortisol. Using cross-sectional analyses, we calculated prevalence ratios (PRs) and 95 % confidence intervals (CI) for the association of any and specific laboratory abnormalities with osteoporosis and the number of men with osteoporosis needed to test to identify one additional laboratory abnormality compared to testing men without osteoporosis. Results: Approximately 60 % of men had ≥1 laboratory abnormality in both men with and without osteoporosis. Among individual tests, only vitamin D insufficiency (PR, 1.13; 95 % CI, 1.05–1.22) and high alkaline phosphatase (PR, 3.05; 95 % CI, 1.52–6.11) were more likely in men with osteoporosis. Hypercortisolism and hyperthyroidism were uncommon and not significantly more frequent in men with osteoporosis. No osteoporotic men had hypercalciuria. Conclusions: Though most of these older men had ≥1 laboratory abnormality, few routinely recommended individual tests were more common in men with osteoporosis than in those without osteoporosis. Possibly excepting vitamin D and alkaline phosphatase, benefit of routine laboratory testing to identify possible secondary causes in older osteoporotic men appears low. Results may not be generalizable to younger men or to older men in whom history and exam findings raise clinical suspicion for a secondary cause of osteoporosis.

Fischer, C. R., Cassilly, R., Dyrszka, M., Trimba, Y., Peters, A., Goldstein, J. A., et al. (2016). Cost-effectiveness of lumbar spondylolisthesis surgery at 2-year follow-up. *Spine Deformity, 4*(1), 48-54.

Objectives The purpose of this study was to determine the cost/quality-adjusted life-year (QALY) of the operative treatment of lumbar spondylolisthesis and identify factors associated with cost-effectiveness at 2 years. Methods We evaluated patients who underwent surgery for spondylolisthesis. The QALY was determined from the EQ5D. Outcomes were also assessed using the Oswestry Disability Index (ODI). Surgical, neuromonitoring, and anesthesia Current Procedural Terminology (CPT) codes as well as hospital Diagnosis-Related Group codes were used to determine the Medicare direct care costs of surgery. Indirect costs were modeled based on existing literature. A discounting rate of 3% was applied. Analysis was performed to determine which factors were associated with a cost/QALY less than $100,000. Results There were 44 patients who underwent surgery for either degenerative (30) or isthmic spondylolisthesis (14). There were 27 women and 17 men, with an average age at surgery of 59.7 years (standard deviation [SD] = 14.69) and an average follow-up of 2 years (SD = 0.82). The average postoperative improvement in ODI was 24.77 (SD = 23.9), and change in QALY was 0.43 (SD = 0.30). The average cost/QALY at 2 years for direct care costs was $89,065. The average cost/QALY at 2 years for direct plus indirect costs was $112,588. Higher preoperative leg pain and greater leg pain change was associated with a cost/QALY <$100,000 ($p < .005$, $p < .028$). The cost-effective group had a higher proportion of patients with disease extent of two or more levels ($p = .021$). When comparing surgical techniques of anterior-posterior and posterior only, there was no difference in cost-effectiveness. Conclusions Spondylolisthesis surgery is cost-effective at 2 years, with a QALY change of 0.43 and a direct cost/QALY of $89,065. Higher preoperative leg pain and larger extent of disease was associated with cost-effectiveness. Level of Evidence IV.

Fischer, J. M., Dudley, S., Miller, A. J., & Liskay, R. M. (2015). An intact Pms2 ATPase domain is not essential for male fertility. *DNA Repair,*

The DNA mismatch repair (MMR) machinery in mammals plays critical roles in both mutation avoidance and spermatogenesis. Meiotic analysis of knockout mice of two different MMR genes,

Mlh1 and Mlh3, revealed both male and female infertility associated with a defect in meiotic crossing over. In contrast, another MMR gene knockout, Pms2 (Pms2ko/ko), which contained a deletion of a portion of the ATPase domain, produced animals that were male sterile but female fertile. However, the meiotic phenotype of Pms2ko/ko males was less clear-cut than for Mlh1- or Mlh3-deficient meiosis. More recently, we generated a different Pms2 mutant allele (Pms2cre), which results in deletion of the same portion of the ATPase domain. Surprisingly, Pms2cre/cre male mice were completely fertile, suggesting that the ATPase domain of Pms2 is not required for male fertility. To explore the difference in male fertility, we examined the Pms2 RNA and found that alternative splicing of the Pms2cre allele results in a predicted Pms2 containing the C-terminus, which contains the Mlh1-interaction domain, a possible candidate for stabilizing Mlh1 levels. To study further the basis of male fertility, we examined Mlh1 levels in testes and found that whereas Pms2 loss in Pms2ko/ko mice results in severely reduced levels of Mlh1 expression in the testes, Mlh1 levels in Pms2cre/cre testes were reduced to a lesser extent. Thus, we propose that a primary function of Pms2 during spermatogenesis is to stabilize Mlh1 levels prior to its critical crossing over function with Mlh3.

Folk, J. C., Adelman, R. A., Flaxel, C. J., Hyman, L., Pulido, J. S., & Olsen, T. W. (2016). Idiopathic epiretinal membrane and vitreomacular traction. *Ophthalmology, 123*(1), P152-P181.

Fombonne, E., Marcin, C., Manero, A. C., Bruno, R., Diaz, C., Villalobos, M., et al. (2016). Prevalence of autism spectrum disorders in guanajuato, mexico: The leon survey. *Journal of Autism and Developmental Disorders,*

There are no epidemiological data on autism for Mexico. This study was conducted to generate a first estimate of ASD prevalence in Mexico. We surveyed children age eight in Leon (Guanajuato). The sample was stratified in two strata: (1) children having special education and medical records (SEMR; N = 432) and (2) children attending regular schools (GSS; N = 11,684). GSS children were screened with the SRS and those with the highest scores were invited to a diagnostic evaluation. The final sample comprised 36 children (80.6 % male) who had confirmed ASD. A third had intellectual disability, 25 % were non-verbal, 69 % had co-occurring behavioral

problems. The prevalence overall was 0.87 % (95 % CI 0.62, 1.1 %). This survey provides an estimate for ASD prevalence in Mexico that is consistent with recent studies.

Fornetti, J., Flanders, K. C., Henson, P. M., Tan, A. -., Borges, V. F., & Schedin, P. (2016). Mammary epithelial cell phagocytosis downstream of TGF-β3 is characterized by adherens junction reorganization. *Cell Death and Differentiation, 23*(2), 185-196.

After weaning, during mammary gland involution, milk-producing mammary epithelial cells undergo apoptosis. Effective clearance of these dying cells is essential, as persistent apoptotic cells have a negative impact on gland homeostasis, future lactation and cancer susceptibility. In mice, apoptotic cells are cleared by the neighboring epithelium, yet little is known about how mammary epithelial cells become phagocytic or whether this function is conserved between species. Here we use a rat model of weaning-induced involution and involuting breast tissue from women, to demonstrate apoptotic cells within luminal epithelial cells and epithelial expression of the scavenger mannose receptor, suggesting conservation of phagocytosis by epithelial cells. In the rat, epithelial transforming growth factor-β (TGF-β) signaling is increased during involution, a pathway known to promote phagocytic capability. To test whether TGF-β enhances the phagocytic ability of mammary epithelial cells, non-transformed murine mammary epithelial EpH4 cells were cultured to achieve tight junction impermeability, such as occurs during lactation. TGF-β3 treatment promoted loss of tight junction impermeability, reorganization and cleavage of the adherens junction protein E-cadherin (E-cad), and phagocytosis. Phagocytosis correlated with junction disruption, suggesting junction reorganization is necessary for phagocytosis by epithelial cells. Supporting this hypothesis, epithelial cell E-cad reorganization and cleavage were observed in rat and human involuting mammary glands. Further, in the rat, E-cad cleavage correlated with increased γ-secretase activity and β-catenin nuclear localization. In vitro, pharmacologic inhibitors of γ-secretase or β-catenin reduced the effect of TGF-β3 on phagocytosis to near baseline levels. However, β-catenin signaling through LiCl treatment did not enhance phagocytic capacity, suggesting a model in which both reorganization of cell junctions and β-catenin signaling contribute to phagocytosis downstream of TGF-β3. Our data provide insight into how mammary epithelial cells contribute to apoptotic cell clearance, and in light of the negative

consequences of impaired apoptotic cell clearance during involution, may shed light on involution-associated breast pathologies. © 2016 Macmillan Publishers Limited. All rights reserved.

Fowler, A., Partridge, K., Chelba, C., Bi, X., Ouyang, T., & Zhai, S. (2015). Effects of language modeling and its personalization on touchscreen typing performance. *33rd Annual CHI Conference on Human Factors in Computing Systems, CHI 2015, , 2015-April.* pp. 649-658. Modern smartphones correct typing errors and learn userspecific words (such as proper names). Both techniques are useful, yet little has been published about their technical specifics and concrete benefits. One reason is that typing accuracy is difficult to measure empirically on a large scale. We describe a closed-loop, smart touch keyboard (STK) evaluation system that we have implemented to solve this problem. It includes a principled typing simulator for generating human-like noisy touch input, a simple-yet-effective decoder for reconstructing typed words from such spatial data, a large web-scale background language model (LM), and a method for incorporating LM personalization. Using the Enron email corpus as a personalization test set, we show for the first time at this scale that a combined spatial/language model reduces word error rate from a pre-model baseline of 38.4% down to 5.7%, and that LM personalization can improve this further to 4.6%. © Copyright 2015 ACM.

Fratzl-Zelman, N., Bachinger, H. P., Vranka, J. A., Roschger, P., Klaushofer, K., & Rauch, F. (2016). Bone matrix hypermineralization in prolyl-3 hydroxylase 1 deficient mice. *Bone, 85*, 15-22. Lack of prolyl 3-hydroxylase 1 (P3H1) due to mutations in P3H1 results in severe forms of recessive osteogenesis imperfecta. In the present study, we investigated the bone tissue characteristics of P3H1 null mice. Histomorphometric analyses of cancellous bone in the proximal tibia and lumbar vertebra in 1-month and 3-month old mice demonstrated that P3H1 deficient mice had low trabecular bone volume and low mineral apposition rate, but normal osteoid maturation time and normal osteoblast and osteoclast surfaces. Quantitative backscattered electron imaging revealed that the bone mineralization density distribution was shifted towards higher values, indicating hypermineralization of bone matrix. It thus appears that P3H1 deficiency leads to decreased deposition of extracellular matrix by osteoblasts and increased incorporation of mineral into the matrix.

Freedland, S. J., Howard, L. E., Hanyok, B. T., Kadiyala, V. K., Kuang, J. Y., Whitney, C. A., et al. (2016). Validation of a bone scan positivity risk table in non-metastatic castration-resistant prostate cancer. *BJU International,*

OBJECTIVES: We have previously developed a risk table to predict the probability of a positive bone scan among men with non-metastatic castrate resistant prostate cancer (M0 CRPC). Herein, we tested its external validity of this risk table in a separate cohort. PATIENTS AND METHODS: We retrospectively analyzed 429 bone scans of 281 CRPC patients with no known prior metastases treated at three Veterans Affairs Medical Centers. We assessed the predictors of a positive scan using generalized estimating equations. Area under the curve (AUC), calibration plots and decision curve analysis were used to assess the performance of our prior model to predict a positive scan in the current data. RESULTS: A total of 113 scans (26%) were positive. On multivariable analysis, the only significant predictors of a positive scan were log-transformed PSA (HR 2.13, 95%CI 1.71-2.66, p<0.001) and log-transformed PSA doubling time (PSADT; HR=0.53, 95%CI 0.41-0.68, p<0.001). Among men with a PSA <5 ng/ml, the rate of positive scans was 5%. The previously developed risk table had an AUC of 0.735 to predict positive bone scan with excellent calibration and provided additional net benefit in the decision curve analysis. CONCLUSIONS: We have validated our previously developed table to predict the risk of a positive bone scan among men with M0/Mx CRPC. Use of this risk table may allow better tailoring of patients' scanning to identify metastases early while minimizing over-imaging. Regardless of PSADT, positive bone scans were rare in men with a PSA <5 ng/ml. This article is protected by copyright. All rights reserved.

Frey, L. C., & Hamilton, B. E. (2014). Seizures. (pp. 133-143) Cambridge University Press.

What is a seizure? Seizures are an important cause of visits to an emergency department (ED), accounting for millions of visits annually worldwide. The billions of neurons in the human brain generally communicate with each other via small electrical and chemical signals. However, when networks of neurons function abnormally, they can produce much larger, synchronous, electrical discharges. In general, these highly synchronized discharges are abnormal and when spontaneous and sustained highly synchronous discharges occur, they disrupt otherwise normal brain activity, creating an electrical seizure in the brain. Because this electrical seizure disrupts

normal brain activity, a person can experience involuntary experiential or behavioral changes that are the clinical manifestations of a seizure. This chapter will focus on patients presenting with clinical manifestations of seizures. Additional information about seizures occurring alongside symptoms due to other conditions can be found in other chapters of this book. In general, these involuntary experiential or behavioral changes are highly dependent on the functions of the brain that are located where the abnormal discharge starts and over the area where the abnormal discharge eventually spreads [1]. For example, a complex partial seizure of mesial temporal onset may begin with the patient experiencing a sensation of an unpleasant smell. As the seizure progresses and the abnormal electrical activity spreads within the brain, patients may stare and have abnormal involuntary, often repetitive, movements of their mouth or hands. Seizures with onsets in different areas of the brain will have different manifestations. A list of common clinical manifestations of seizures, along with their suspected regions of onset, can be found in Table 8.1.

Gardner, R. T., Ripplinger, C. M., Myles, R. C., & Habecker, B. A. (2016). Molecular mechanisms of sympathetic remodeling and arrhythmias. *Circulation.Arrhythmia and Electrophysiology, 9*(2), e001359.

Garzotto, M., & Kopp, R. P. (2016). Gene-expression profiling of localized prostate cancer: Still miles to go before we sleep. *Future Oncology (London, England), 12*(3), 273-276.

Gayet-Primo, J., & Puthussery, T. (2015). Alterations in kainate receptor and TRPM1 localization in bipolar cells after retinal photoreceptor degeneration. *Frontiers in Cellular Neuroscience, 9*, 486. Photoreceptor degeneration differentially impacts glutamatergic signaling in downstream On and Off bipolar cells. In rodent models, photoreceptor degeneration leads to loss of glutamatergic signaling in On bipolar cells, whereas Off bipolar cells appear to retain glutamate sensitivity, even after extensive photoreceptor loss. The localization and identity of the receptors that mediate these residual glutamate responses in Off bipolar cells have not been determined. Recent studies show that macaque and mouse Off bipolar cells receive glutamatergic input primarily through kainate-type glutamate receptors. Here, we studied the impact of photoreceptor degeneration on glutamate receptor and their associated proteins in Off and On bipolar cells. We show that the

kainate receptor subunit, GluK1, persists in remodeled Off bipolar cell dendrites of the rd10 mouse retina. However, the pattern of expression is altered and the intensity of staining is reduced compared to wild-type retina. The kainate receptor auxiliary subunit, Neto1, also remains in Off bipolar cell dendrites after extensive photoreceptor degeneration. Similar preservation of kainate receptor subunits was evident in human retina in which photoreceptors had degenerated due to serous retinal detachment. In contrast, photoreceptor degeneration leads to loss of synaptic expression of TRPM1 in mouse and human On bipolar cells, but strong somatic expression remains. These findings demonstrate that Off bipolar cells retain dendritic glutamate receptors during retinal degeneration and could thus serve as a conduit for signal transmission from transplanted or optogenetically restored photoreceptors.

Gebara, M. A., Lipsey, K. L., Karp, J. F., Nash, M. C., Iaboni, A., & Lenze, E. J. (2015). Cause or effect? selective serotonin reuptake inhibitors and falls in older adults: A systematic review. *American Journal of Geriatric Psychiatry, 23*(10), 1016-1028.

A 2012 update of the Beers criteria categorizes selective serotonin reuptake inhibitors (SSRIs) as potentially inappropriate medications in all older adults based on fall risk. The application of these recommendations, not only to frail nursing home residents, but to all older adults, may lead to changes in health policy or clinical practice with harmful consequences. A systematic review of studies on the association between SSRIs and falls in older adults was conducted to examine the evidence for causation. Twenty-six studies met the inclusion criteria. The majority of studies were observational and suggest an association between SSRIs and falls. The direction of the relationship - causation or effect - cannot be discerned from this type of study. Standardized techniques for determining likely causation were then used to see if there was support for the hypothesis that SSRIs lead to falls. This analysis did not suggest causation was likely. There is no Level 1 evidence that SSRIs cause falls. Therefore, changes in the current treatment guidelines or policies on the use of SSRIs in older adults based on fall risk may not be justified at this time given the lack of an established evidence base. Given its significance to public health, well-designed experimental studies are required to address this question definitively.

Geiger, K. E., Koeller, D. M., Harding, C. O., Huntington, K. L., & Gillingham, M. B. (2016). Normal vitamin D levels and bone mineral density among children with inborn errors of metabolism consuming medical food-based diets. *Nutrition Research, 36*(1), 101-108.

A higher incidence of osteopenia is observed among children with inherited metabolic disorders (inborn errors of metabolism, or IEMs) who consume medical food-based diets that restrict natural vitamin D-containing food sources. We evaluated the vitamin D status of children with IEMs who live in the Pacific Northwest with limited sun exposure and determined whether bone mineral density (BMD) in children with phenylketonuria (PKU), the most common IEM, correlated with diet or biochemical markers of bone metabolism. We hypothesized that children with IEMs would have lower serum vitamin D concentrations than controls and that some children with PKU would have reduced bone mineralization. A retrospective record review of 88 patients with IEMs, and 445 children on unrestricted diets (controls) found the 25-hydroxyvitamin D concentrations were normal and not significantly different between groups (IEM patients, 27.1 ± 10.9; controls, 27.6 ± 11.2). Normal BMD at the hip or spine (-2 < z score < 2) was measured in 20 patients with PKU. There was a correlation between lumbar spine BMD and dietary calcium intake. We saw no evidence of low serum vitamin D in our population of children with IEMs compared with control children. We also found no evidence for reduced BMD in children with PKU on specialized diets, but BMD was associated with calcium intake. Dietary intake of essential nutrients in medical food-based diets supports normal 25-hydroxyvitamin D levels and BMD in children with IEMs, including PKU. The risk of vitamin D deficiency among patients consuming a medical food-based diet is similar to the general population. © 2016 Elsevier Inc.

Gerstein, N. S., Gerstein, W. H., Carey, M. C., Kong Lam, N. C., Ram, H., Spassil, N. R., et al. (2015). Erratum: The thrombotic and arrhythmogenic risks of perioperative NSAIDs(J cardiothorac vasc anesth(2014):28:369-378). *Journal of Cardiothoracic and Vascular Anesthesia, 29*(4), e38.

Gessner, B. D., Wood, T., Johnson, M. A., Richards, C. S., & Koeller, D. M. (2016). Evidence for an association between infant mortality and homozygosity for the arctic variant of carnitine palmitoyltransferase 1A. *Genetics in Medicine : Official Journal of the American College of Medical Genetics,*

PURPOSE: Infant mortality in Alaska is highest among Alaska Native people from western/northern Alaska, a population with a high prevalence of a genetic variant (c.1436C>T; the arctic variant) of carnitine palmitoyltransferase 1A (CPT1A). METHODS: We performed an unmatched case-control study to determine the relationship between the arctic variant and infant mortality. The cases were 110 Alaska Native infant deaths from 2006 to 2010 and the controls were 395 Alaska Native births from the same time period. In addition to the overall analysis, we conducted two subanalyses, one limited to subjects from western/northern Alaska and one limited to infants heterozygous or homozygous for the arctic variant. RESULTS: Among western/northern Alaska residents, 66% of cases and 61% of controls were homozygous (adjusted odds ratio (aOR): 2.5; 95% confidence interval (CI): 1.3, 5.0). Among homozygous or heterozygous infants, 58% of cases and 44% of controls were homozygous (aOR: 2.3; 95% CI: 1.3, 4.0). Deaths associated with infection were more likely to be homozygous (OR: 2.9; 95% CI: 1.0-8.0). Homozygosity was strongly associated with a premorbid history of pneumonia, sepsis, or meningitis. CONCLUSION: Homozygosity for the arctic variant is associated with increased risk of infant mortality, which may be mediated in part by an increase in infectious disease risk. Further studies are needed to determine whether the association we report represents a causal association between the CPT1A arctic variant and infectious disease-specific mortality.Genet Med advance online publication 28 January 2016Genetics in Medicine (2016); doi:10.1038/gim.2015.197.

Gesuete, R., Christensen, S. N., Bahjat, F. R., Packard, A. E. B., Stevens, S. L., Liu, M., et al. (2016). Cytosolic receptor melanoma differentiation-associated protein 5 mediates preconditioning-induced neuroprotection against cerebral ischemic injury. *Stroke, 47*(1), 262-266.
Background and Purpose - Preconditioning with poly-l-lysine and carboxymethylcellulose (ICLC) provides robust neuroprotection from cerebral ischemia in a mouse stroke model. However, the receptor that mediates neuroprotection is unknown. As a synthetic double-stranded RNA, poly-ICLC may bind endosomal Toll-like receptor 3 or one of the cytosolic retinoic acid-inducible gene-I-like receptor family members, retinoic acid-inducible gene-I, or melanoma differentiation-associated protein 5. Activation of these receptors culminates in type I interferons (IFN-α/β) induction - a response required for poly-ICLC-induced neuroprotection. In this study, we

investigate the receptor required for poly-ICLC-induced neuroprotection. Methods - Toll-like receptor 3, melanoma differentiation-associated protein 5-, and IFN-promoter stimulator 1-deficient mice were treated with poly-ICLC 24 hours before middle cerebral artery occlusion. Infarct volume was measured 24 hours after stroke to identify the receptor signaling pathways involved in protection. IFN-α/β induction was measured in plasma samples collected 6 hours after poly-ICLC treatment. IFN-β-deficient mice were used to test the requirement of IFN-β for poly-ICLC-induced neuroprotection. Mice were treated with recombinant IFN-α-A to test the role of IFN-α as a potential mediator of neuroprotection. Results - Poly-ICLC induction of both neuroprotection and systemic IFN-α/β requires the cytosolic receptor melanoma differentiation-associated protein 5 and the adapter molecule IFN-promoter stimulator 1, whereas it is independent of Toll-like receptor 3. IFN-β is not required for poly-ICLC-induced neuroprotection. IFN-α treatment protects against stroke. Conclusions - Poly-ICLC preconditioning is mediated by melanoma differentiation-associated protein 5 and its adaptor molecule IFN-promoter stimulator 1. This is the first evidence that a cytosolic receptor can mediate neuroprotection, providing a new target for the development of therapeutic agents to protect the brain from ischemic injury.

Giunzioni, I., Tavori, H., Covarrubias, R., Major, A. S., Ding, L., Zhang, Y., et al. (2016). Local effects of human PCSK9 on the atherosclerotic lesion. *Journal of Pathology, 238*(1), 52-62.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes atherosclerosis by increasing low-density lipoprotein (LDL) cholesterol levels through degradation of hepatic LDL receptor (LDLR). Studies have described the systemic effects of PCSK9 on atherosclerosis, but whether PCSK9 has local and direct effects on the plaque is unknown. To study the local effect of human PCSK9 (hPCSK9) on atherosclerotic lesion composition, independently of changes in serum cholesterol levels, we generated chimeric mice expressing hPCSK9 exclusively from macrophages, using marrow from hPCSK9 transgenic (hPCSK9tg) mice transplanted into apoE-/- and LDLR-/- mice, which were then placed on a high-fat diet (HFD) for 8 weeks. We further characterized the effect of hPCSK9 expression on the inflammatory responses in the spleen and by mouse peritoneal macrophages (MPM) in vitro. We found that MPMs from transgenic mice express both murine (m) Pcsk9 and hPCSK9 and that the latter reduces macrophage LDLR and

LRP1 surface levels. We detected hPCSK9 in the serum of mice transplanted with hPCSK9tg marrow, but did not influence lipid levels or atherosclerotic lesion size. However, marrow-derived PCSK9 progressively accumulated in lesions of apoE-/- recipient mice, while increasing the infiltration of Ly6Chi inflammatory monocytes by 32% compared with controls. Expression of hPCSK9 also increased CD11b- and Ly6Chi-positive cell numbers in spleens of apoE-/- mice. In vitro, expression of hPCSK9 in LPS-stimulated macrophages increased mRNA levels of the pro-inflammatory markers TNF and Il1b (40% and 45%, respectively) and suppressed those of the anti-inflammatory markers Il10 and Arg1 (30% and 44%, respectively). All PCSK9 effects were LDLR-dependent, as PCSK9 protein was not detected in lesions of LDLR-/- recipient mice and did not affect macrophage or splenocyte inflammation. In conclusion, PCSK9 directly increases atherosclerotic lesion inflammation in an LDLR-dependent but cholesterol-independent mechanism, suggesting that therapeutic PCSK9 inhibition may have vascular benefits secondary to LDL reduction.

Goldstein, J. L., Whellan, D. J., Scheiman, J. M., Cryer, B. L., Eisen, G. M., Lanas, A., et al. (2016). Long-term safety of a coordinated delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg for secondary cardiovascular disease prevention in patients at GI risk. *Cardiovascular Therapeutics,*

INTRODUCTIO: In two, 6-month, randomized, double-blind Phase 3 trials, PA32540 (enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) compared to aspirin alone was associated with fewer endoscopic gastric and duodenal ulcers in patients requiring aspirin therapy for secondary cardiovascular disease (CVD) prevention who were at risk for upper gastrointestinal (UGI) events. AIMS: In this 12-month, open-label, multicenter Phase 3 study, we evaluated the long-term cardiovascular and gastrointestinal safety of PA32540 in subjects who were taking aspirin 325 mg daily for >/=3 months for secondary CVD prevention and were at risk for aspirin-associated UGI events. Enrolled subjects received PA32540 once daily for up to 12 months, and were assessed at Baseline, Month 1, Month 6, and Month 12. RESULTS: The overall safety population consisted of 379 subjects and 290 subjects (76%) were on PA32540 for >/=348 days (12-month completers). Adverse events (AEs) caused study withdrawal in 13.5% of subjects,

most commonly gastroesophageal reflux disease (1.1%). Treatment-emergent AEs occurred in 76% of the safety population (11% treatment-related) and 73% of 12-month completers (8% treatment-related). The most common treatment-related AE was dyspepsia (2%). One subject had a gastric ulcer observed on for-cause endoscopy. There were 5 cases of adjudicated non-fatal myocardial infarction, 1 non-fatal stroke, and 1 cardiovascular death, but none considered treatment-related. CONCLUSIONS: Long-term treatment with PA32540 once daily for up to 12 months in subjects at risk for aspirin-associated UGI events is not associated with any new or unexpected safety events. Clinical trials. gov identifier: NCT00995410.

Goodspeed, A., Heiser, L. M., Gray, J. W., & Costello, J. C. (2016). Tumor-derived cell lines as molecular models of cancer pharmacogenomics. *Molecular Cancer Research, 14*(1), 3-13. Compared with normal cells, tumor cells have undergone an array of genetic and epigenetic alterations. Often, these changes underlie cancer development, progression, and drug resistance, so the utility of model systems rests on their ability to recapitulate the genomic aberrations observed in primary tumors. Tumor-derived cell lines have long been used to study the underlying biologic processes in cancer, as well as screening platforms for discovering and evaluating the efficacy of anticancer therapeutics. Multiple -omic measurements across more than a thousand cancer cell lines have been produced following advances in high-throughput technologies and multigroup collaborative projects. These data complement the large, international cancer genomic sequencing efforts to characterize patient tumors, such as The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC). Given the scope and scale of data that have been generated, researchers are now in a position to evaluate the similarities and differences that exist in genomic features between cell lines and patient samples. As pharmacogenomics models, cell lines offer the advantages of being easily grown, relatively inexpensive, and amenable to high-throughput testing of therapeutic agents. Data generated from cell lines can then be used to link cellular drug response to genomic features, where the ultimate goal is to build predictive signatures of patient outcome. This review highlights the recent work that has compared -omic profiles of cell lines with primary tumors, and

discusses the advantages and disadvantages of cancer cell lines as pharmacogenomic models of anticancer therapies. ©2015 AACR.

Gorman, K., Olson, L., Hill, A. P., Lunsford, R., Heeman, P. A., & van Santen, J. P. (2016). Uh and um in children with autism spectrum disorders or language impairment. *Autism Research : Official Journal of the International Society for Autism Research,*

Atypical pragmatic language is often present in individuals with autism spectrum disorders (ASD), along with delays or deficits in structural language. This study investigated the use of the "fillers" uh and um by children ages 4-8 during the autism diagnostic observation schedule. Fillers reflect speakers' difficulties with planning and delivering speech, but they also serve communicative purposes, such as negotiating control of the floor or conveying uncertainty. We hypothesized that children with ASD would use different patterns of fillers compared to peers with typical development or with specific language impairment (SLI), reflecting differences in social ability and communicative intent. Regression analyses revealed that children in the ASD group were much less likely to use um than children in the other two groups. Filler use is an easy-to-quantify feature of behavior that, in concert with other observations, may help to distinguish ASD from SLI. Autism Res 2016. (c) 2016 International Society for Autism Research, Wiley Periodicals, Inc.

Graff, J. N., & Beer, T. M. (2015). Metastatic prostate cancer in 2015: The new and the old that is new again. *Nature Reviews Clinical Oncology,*

Graham, B. S., Knight, G. W., & Graham, L. (2016). Dental student academic integrity in U.S. dental schools: Current status and recommendations for enhancement. *Journal of Dental Education, 80*(1), 5-13.

Cheating incidents in 2006-07 led U.S. dental schools to heighten their efforts to enhance the environment of academic integrity in their institutions. The aims of this study were to document the measures being used by U.S. dental schools to discourage student cheating, determine the current incidence of reported cheating, and make recommendations for enhancing a culture of integrity in dental education. In late 2014-early 2015, an online survey was distributed to academic deans of all 61 accredited U.S. dental schools that had four classes of dental students enrolled; 50 (82%) responded. Among measures used, 98% of respondents reported having

policy statements regarding student academic integrity, 92% had an Honor Code, 96% provided student orientation to integrity policies, and most used proctoring of final exams (91%) and tests (93%). Regarding disciplinary processes, 27% reported their faculty members only rarely reported suspected cheating (though required in 76% of the schools), and 40% disseminated anonymous results of disciplinary hearings. A smaller number of schools (n=36) responded to the question about student cheating than to other questions; those results suggested that reported cheating had increased almost threefold since 1998. The authors recommend that schools add cheating case scenarios to professional ethics curricula; disseminate outcomes of cheating enforcement actions; have students sign a statement attesting to compliance with academic integrity policies at every testing activity; add curricular content on correct writing techniques to avoid plagiarism; require faculty to distribute retired test items; acquire examination-authoring software programs to enable faculty to generate new multiple-choice items and different versions of the same multiple-choice tests; avoid take-home exams when assessing independent student knowledge; and utilize student assessment methods directly relevant to clinical practice.

Greenberg, G. D., Huang, L. C., Spence, S. E., Schlumbohm, J. P., Metten, P., Ozburn, A. R., et al. (2016). Nest building is a novel method for indexing severity of alcohol withdrawal in mice. *Behavioural Brain Research, 302*, 182-190.

Withdrawal after chronic ethanol (EtOH) affects body temperature, goal-directed behavior and motor function in mice and increases general central nervous system excitability. Nest-building tests have been used to assay these states but to this point have not been employed as measures of EtOH withdrawal severity. We first refined nest-scoring methods using a genetically heterogeneous stock of mice (HS/Npt). Mice were then made physically dependent following three days of chronic EtOH vapor inhalation to produce average blood EtOH concentrations (BECs) of 1.89mg/mL. EtOH withdrawal affected the progression of nest building over time when mice were tested 2-4 days after removal from three days of chronic exposure to EtOH. In a separate group of mice, chronic EtOH vapor inhalation (BECs 1.84mg/mL) suppressed nest building over days 1-2 but not days 2-3 of withdrawal. In a following experiment, EtOH withdrawal dose-dependently slowed recovery of nest building for up to 32h. Finally, we determined that long-lasting nest-building deficits extend to mice undergoing withdrawal from a

high dose (4g/kg) of acute EtOH. Sex differences for nest building were absent following EtOH exposure. In mice naive to EtOH treatments, male mice had lower pre-test body temperatures and increased nest scores across a two-day testing period compared to females. These results suggest that nest building can be used to assess chronic and acute EtOH withdrawal severity in mice.

Grigsby, P. L. (2016). Animal models to study placental development and function throughout normal and dysfunctional human pregnancy. *Seminars in Reproductive Medicine, 34*(1), 11-16.
Abnormalities of placental development and function are known to underlie many pathologies of pregnancy, including spontaneous preterm birth, fetal growth restriction, and preeclampsia. A growing body of evidence also underscores the importance of placental dysfunction in the lifelong health of both mother and offspring. However, our knowledge regarding placental structure and function throughout pregnancy remains limited. Understanding the temporal growth and functionality of the human placenta throughout the entirety of gestation is important if we are to gain a better understanding of placental dysfunction. The utilization of new technologies and imaging techniques that could enable safe monitoring of placental growth and function in vivo has become a major focus area for the National Institutes of Child Health and Human Development, as evident by the establishment of the "Human Placenta Project." Many of the objectives of the Human Placenta Project will necessitate preclinical studies and testing in appropriately designed animal models that can be readily translated to the clinical setting. This review will describe the advantages and limitations of relevant animals such as the guinea pig, sheep, and nonhuman primate models that have been used to study the role of the placenta in fetal growth disorders, preeclampsia, or other maternal diseases during pregnancy.

Guimarães-Souza, E. M., Perche, O., Morgans, C. W., Duvoisin, R. M., & Calaza, K. C. (2016). Fragile X mental retardation protein expression in the retina is regulated by light. *Experimental Eye Research, 146*, 72-82.
Fragile X Mental Retardation Protein (FMRP) is a RNA-binding protein that modulates protein synthesis at the synapse and its function is regulated by glutamate. The retina is the first structure that participates in vision, and uses glutamate to transduce electromagnetic signals

from light to electrochemical signals to neurons. FMRP has been previously detected in the retina, but its localization has not been studied yet. In this work, our objectives were to describe the localization of FMRP in the retina, to determine whether different exposure to dark or light stimulus alters FMRP expression in the retina, and to compare the pattern in two different species, the mouse and chick. We found that both FMRP mRNA and protein are expressed in the retina. By immunohistochemistry analysis we found that both mouse and chick present similar FMRP expression localized mainly in both plexiform layers and the inner retina. It was also observed that FMRP is down-regulated by 24 h dark adaptation compared to its expression in the retina of animals that were exposed to light for 1 h after 24 h in the dark. We conclude that FMRP is likely to participate in retinal physiology, since its expression changes with light exposure. In addition, the expression pattern and regulation by light of FMRP seems well conserved since it was similar in both mouse and chick. © 2015 Elsevier Ltd.

Gumus Balikcioglu, P., Balikcioglu, M., Muehlbauer, M. J., Purnell, J. Q., Broadhurst, D., Freemark, M., et al. (2015). Macronutrient regulation of ghrelin and peptide YY in pediatric obesity and prader-willi syndrome. *The Journal of Clinical Endocrinology and Metabolism, 100*(10), 3822-3831. BACKGROUND: The roles of macronutrients and GH in the regulation of food intake in pediatric obesity and Prader-Willi Syndrome (PWS) are poorly understood. OBJECTIVE: We compared effects of high-carbohydrate (HC) and high-fat (HF) meals and GH therapy on ghrelin, insulin, peptide YY (PYY), and insulin sensitivity in children with PWS and body mass index (BMI) -matched obese controls (OCs). METHODS: In a randomized, crossover study, 14 PWS (median, 11.35 y; BMI z score [BMI-z], 2.15) and 14 OCs (median, 11.97 y; BMI-z, 2.35) received isocaloric breakfast meals (HC or HF) on separate days. Blood samples were drawn at baseline and every 30 minutes for 4 hours. Mixed linear models were adjusted for age, sex, and BMI-z. RESULTS: Relative to OCs, children with PWS had lower fasting insulin and higher fasting ghrelin and ghrelin/PYY. Ghrelin levels were higher in PWS across all postprandial time points ($P < .0001$). Carbohydrate was more potent than fat in suppressing ghrelin levels in PWS ($P = .028$); HC and HF were equipotent in OCs but less potent than in PWS ($P = .011$). The increase in PYY following HF was attenuated in PWS ($P = .037$); thus, postprandial ghrelin/PYY remained higher throughout. A lesser increase in insulin and lesser decrease in ghrelin were observed in GH-

treated PWS patients than in untreated patients; PYY responses were comparable. CONCLUSION: Children with PWS have fasting and postprandial hyperghrelinemia and an attenuated PYY response to fat, yielding a high ghrelin/PYY ratio. GH therapy in PWS is associated with increased insulin sensitivity and lesser postprandial suppression of ghrelin. The ratio Ghrelin/PYY may be a novel marker of orexigenic drive.

Hahn, N. M., Knudsen, B. S., Daneshmand, S., Koch, M. O., Bihrle, R., Foster, R. S., et al. (2016). Neoadjuvant dasatinib for muscle-invasive bladder cancer with tissue analysis of biologic activity. *Urologic Oncology: Seminars and Original Investigations, 34*(1), 4.e11-4.e17.
Objectives: Preclinical urothelial carcinoma models suggest activity of dasatinib, an oral SRC-family kinase (SFK) inhibitor. We sought to determine the feasibility and biologic activity of neoadjuvant dasatinib (Neo-D) in patients with muscle-invasive urothelial carcinoma of the bladder (miUCB) preceding radical cystectomy (RC). Materials and methods: A prospective multisite phase II trial was conducted. Key eligibility criteria included: resectable miUCB (T2-T4a, N0, M0), and Eastern Cooperative Oncology Group performance status 0 to 1. Patients received oral Neo-D 100. mg once daily for 28±7 days followed by RC 8 to 24 hours after the last dose. The primary end point was feasibility, defined as≥60% of patients with miUCB completing therapy without treatment-related dose-limiting toxicity (DLT). Pre- and posttreatment tumor immunohistochemistry of phosphorylated SFK (pSFK), Ki-67, and cleaved caspase (Cas)-3 results were analyzed by paired t test. Results: The study completed full accrual with enrollment of 25 patients of whom 23 were evaluable for feasibility. The study achieved its primary end point with 15 patients (65%) completing therapy without treatment-related DLTs. DLTs included: fatigue (n = 2), pulmonary embolism, abdominal pain, supraventricular tachycardia, enteric fistula, hematuria, and dyspnea (n = 1 each). At RC, 5 patients (23%) had<pT2 disease. Analysis of pre- and posttreatment tumors demonstrated significantly decreased pSFK (P = 0.003) but no overall significant changes in Ki-67 or Cas3. In total, 4 cases demonstrated a nonsignificant decrease in Ki-67, of which 3 cases also demonstrated a decrease in pSFK and 2 cases had marginal increase in Cas3. Conclusions: Neo-D in miUCB patients was feasible and safe. Overall, significant inhibition of pSFK was observed without overall reduction of cellular proliferation or increase of apoptosis, although biologic anti-tumor activity may exist in a small subset of patients. These

results highlight the potential utility of the neoadjuvant trial paradigm and suggest that clinical benefit of single-agent SFK inhibition in unselected patients with miUCB is unlikely. © 2016 Elsevier Inc.

Hall, T., Kriz, D., Duvall, S., Nguyen-Driver, M., & Duffield, T. (2015). Healthcare transition challenges faced by young adults with autism spectrum disorder. *Clinical Pharmacology and Therapeutics, 98*(6), 573-575.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impacts communicative interactions, with patterns of repetitive and restricted behaviors, interests, and cognitive rigidity. Recent incidence rate estimates for ASD are 1 in 68, and primarily male (4:1). A major epidemiological issue in ASD is transitioning to independence in adulthood, particularly navigating the healthcare system. This commentary will focus on approaches healthcare providers can use to not overlook and support individuals with ASD. © 2015 ASCPT.

Hammoudeh, M., Al Rayes, H., Alawadhi, A., Gado, K., Shirazy, K., & Deodhar, A. (2015). Clinical assessment and management of spondyloarthritides in the middle east: A multinational investigation. *International Journal of Rheumatology, 2015*, 178750.

Data on spondyloarthritis (SpA) from the Middle East are sparse and the management of these diseases in this area of the world faces a number of challenges, including the relevant resources to enable early diagnosis and referral and sufficient funds to aid the most appropriate treatment strategy. The objective was to report on the characteristics, disease burden, and treatment of SpA in the Middle East region and to highlight where management strategies could be improved, with the overall aim of achieving better patient outcomes. This multicenter, observational, cross-sectional study collected demographic, clinical, laboratory, and treatment data on 169 consecutive SpA patients at four centers (Egypt, Kuwait, Qatar, and Saudi Arabia). The data collected presents the average time from symptom onset to diagnosis along with the presence of comorbidities in the region and comparisons between treatment with NSAIDs and biologics. In the absence of regional registries of SpA patients, the data presented here provide a rare snapshot of the characteristics, disease burden, and treatment of these patients, highlighting the management challenges in the region.

Hansen, M., Meckler, G., Lambert, W., Dickinson, C., Dickinson, K., & Guise, J. M. (2015). Paramedic assessment and treatment of upper airway obstruction in pediatric patients: An exploratory analysis by the children's safety initiative-emergency medical services. *The American Journal of Emergency Medicine,*

Hansen, S. G., Wu, H. L., Burwitz, B. J., Hughes, C. M., Hammond, K. B., Ventura, A. B., et al. (2016). Broadly targeted CD8+ T cell responses restricted by major histocompatibility complex E. *Science (New York, N.Y.),*

Major histocompatibility complex (MHC)-E is a highly conserved, ubiquitously expressed, non-classical MHC-Ib molecule with limited polymorphism primarily involved in NK cell regulation. We found that vaccination of rhesus macaques (RM) with DeltaRh157.5/.4 Rhesus Cytomegalovirus (RhCMV) vectors results in MHC-E-restricted presentation of highly varied peptide epitopes to CD8alpha/beta+ T cells, approximately 4 distinct epitopes per 100 amino acids in all tested antigens. Computational structural analysis revealed that MHC-E provides heterogeneous chemical environments for diverse side chain interactions within a stable, open binding groove. Since MHC-E is up-regulated on cells infected with HIV/SIV and other persistent viruses to evade NK cell activity, MHC-E-restricted CD8+ T cell responses have the potential to exploit pathogen immune evasion adaptations, a capability that might endow these unconventional responses with superior efficacy.

Hanyok, B. T., Howard, L. E., Amling, C. L., Aronson, W. J., Cooperberg, M. R., Kane, C. J., et al. (2016). Is computed tomography a necessary part of a metastatic evaluation for castration-resistant prostate cancer? results from the shared equal access regional cancer hospital database. *Cancer, 122*(2), 222-229.

BACKGROUND Metastatic lesions in prostate cancer beyond the bone have prognostic importance and affect clinical therapeutic decisions. Few data exist regarding the prevalence of soft-tissue metastases at the initial diagnosis of metastatic castration-resistant prostate cancer (mCRPC). METHODS This study analyzed 232 men with nonmetastatic (M0) castration-resistant prostate cancer (CRPC) who developed metastases detected by a bone scan or computed tomography (CT). All bone scans and CT scans within the 30 days before or after the mCRPC diagnosis were

reviewed. The rate of soft-tissue metastases among those undergoing CT was determined. Then, predictors of soft-tissue metastases and visceral and lymph node metastases were identified. RESULTS Compared with men undergoing CT (n = 118), men undergoing only bone scans (n = 114) were more likely to have received primary treatment (P =.048), were older (P =.013), and less recently developed metastases (P =.018). Among those undergoing CT, 52 (44%) had soft-tissue metastases, including 20 visceral metastases (17%) and 41 lymph node metastases (35%), whereas 30% had no bone involvement. In a univariable analysis, only prostate-specific antigen (PSA) predicted soft-tissue metastases (odds ratio [OR], 1.27; P =.047), and no statistically significant predictors of visceral metastases were found. A higher PSA level was associated with an increased risk of lymph node metastases (OR, 1.38; P =.014), whereas receiving primary treatment was associated with decreased risk (OR, 0.36; P =.015). CONCLUSIONS The data suggest that there is a relatively high rate of soft-tissue metastasis (44%) among CRPC patients undergoing CT at the initial diagnosis of metastases, including some men with no bone involvement. Therefore, forgoing CT during a metastatic evaluation may lead to an underdiagnosis of soft-tissue metastases and an underdiagnosis of metastases in general. © 2015 American Cancer Society.

Hassan, S., Petrella, T. M., Zhang, T., Kamel-Reid, S., Nordio, F., Baccarelli, A., et al. (2015). Erratum to: Pathologic complete response to intralesional interleukin-2 therapy associated with improved survival in melanoma patients with in-transit disease (ANN SURG ONCOL, DOI 10.1245/S10434-014-4199-Z). *Annals of Surgical Oncology, 22*, 1603.

Haugen, B. R., Alexander, E. K., Bible, K. C., Doherty, G. M., Mandel, S. J., Nikiforov, Y. E., et al. (2016). 2015 american thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid, 26*(1), 1-133.
Background: Thyroid nodules are a common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent. Since the American Thyroid Association's (ATA's) guidelines for the management of these disorders were revised in 2009, significant scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, researchers,

and health policy makers on published evidence relating to the diagnosis and management of thyroid nodules and differentiated thyroid cancer. Methods: The specific clinical questions addressed in these guidelines were based on prior versions of the guidelines, stakeholder input, and input of task force members. Task force panel members were educated on knowledge synthesis methods, including electronic database searching, review and selection of relevant citations, and critical appraisal of selected studies. Published English language articles on adults were eligible for inclusion. The American College of Physicians Guideline Grading System was used for critical appraisal of evidence and grading strength of recommendations for therapeutic interventions. We developed a similarly formatted system to appraise the quality of such studies and resultant recommendations. The guideline panel had complete editorial independence from the ATA. Competing interests of guideline task force members were regularly updated, managed, and communicated to the ATA and task force members. Results: The revised guidelines for the management of thyroid nodules include recommendations regarding initial evaluation, clinical and ultrasound criteria for fine-needle aspiration biopsy, interpretation of fine-needle aspiration biopsy results, use of molecular markers, and management of benign thyroid nodules. Recommendations regarding the initial management of thyroid cancer include those relating to screening for thyroid cancer, staging and risk assessment, surgical management, radioiodine remnant ablation and therapy, and thyrotropin suppression therapy using levothyroxine. Recommendations related to long-term management of differentiated thyroid cancer include those related to surveillance for recurrent disease using imaging and serum thyroglobulin, thyroid hormone therapy, management of recurrent and metastatic disease, consideration for clinical trials and targeted therapy, as well as directions for future research. Conclusions: We have developed evidence-based recommendations to inform clinical decision-making in the management of thyroid nodules and differentiated thyroid cancer. They represent, in our opinion, contemporary optimal care for patients with these disorders.

Hefti, M. M., Cryan, J. B., Haas, E. A., Chadwick, A. E., Crandall, L. A., Trachtenberg, F. L., et al. (2016). Hippocampal malformation associated with sudden death in early childhood: A neuropathologic study: Part 2 of the investigations of the san diego SUDC research project.

Forensic Science, Medicine, and Pathology, , 1-12.

Purpose: Sudden unexplained death in childhood (SUDC), while rare, accounts for an important fraction of unexpected deaths in children >1 year of age. Previously we reported an association between febrile seizures, hippocampal maldevelopment, and sudden, unexpected deaths in young children (1–6 years), termed "hippocampal maldevelopment associated with sudden death (HMASD)." Here, we characterize in greater detail the hippocampal pathology in a large cohort of cases (n = 42) of this entity, and attempt to define possible new entities responsible for sudden, unexplained death in young children without HMASD/febrile seizure phenotypes. Methods: We performed comparative analysis on cases, which we classified in a cohort of 89 sudden and unexpected deaths as HMASD, explained deaths, SUDC with febrile seizure phenotype (SUDC-FS) but without hippocampal pathology, and SUDC (without hippocampal pathology or febrile seizure phenotype). Results: The frequency of each subgroup was: HMASD 48 % (40/83); SUDC 27 % (22/83); SUDC-FS 18 % (15/83); explained 7 % (6/83). HMASD was characterized clinically by sudden, sleep-related death, term birth, and discovery in the prone position. Key morphologic features of HMASD were focal granule cell bilamination of the dentate gyrus with or without asymmetry and/or malrotation of the hippocampus, associated with significantly increased frequencies of 11 other developmental abnormalities. We identified no other distinct phenotype in the unexplained categories, except for an association of febrile seizures without hippocampal maldevelopment. Conclusions: HMASD is a distinct clinicopathologic entity characterized by a likely developmental failure of neuronal migration in the dentate gyrus. Future research is needed to determine the causal role of HMASD in sudden death in early childhood. © 2016 Springer Science+Business Media New York

Hefti, M. M., Kinney, H. C., Cryan, J. B., Haas, E. A., Chadwick, A. E., Crandall, L. A., et al. (2016). Sudden unexpected death in early childhood: General observations in a series of 151 cases: Part 1 of the investigations of the san diego SUDC research project. *Forensic Science, Medicine, and Pathology,* , 1-10.

Purpose: The purpose of this study was to determine the major subcategories and clinicopathologic features of sudden unexpected death in young children in a large retrospective cohort, and to confirm the association of sudden unexplained death in children (abbreviated by us

for unexplained deaths as SUDC) with hippocampal pathology and/or febrile seizures. Methods: We undertook analysis of a retrospective cohort of 151 cases, of which 80 % (121/151) were subclassified as SUDC, 11 % (16/151) as explained, 7 % (10/151) as undetermined, and 3 % (4/151) as seizure-related. Results: There were no significant differences between SUDC and explained cases in postnatal, gestational, or postconceptional age, frequency of preterm birth, gender, race, or organ weights. In contrast, 96.7 % (117/121) of the SUDC group were discovered during a sleep period compared to 53.3 % (8/15) of the explained group ($p < 0.001$), and 48.8 % (59/121) of the SUDC cases had a personal and/or family history of febrile seizures compared to 6.7 % (1/15) of the explained group ($p < 0.001$). Of the explained deaths, 56 % (9/16) were subclassified as infection, 31 % (5/16) cardiac, 6 % (1/16) accidental, and 6 % (1/16) metabolic. Two of the three cases specifically tested for cardiac channelopathies at autopsy based upon clinical indications had genetic variants in cardiac genes, one of uncertain significance. Bacterial cultures at autopsy typically revealed organisms interpreted as contaminants. Two of the four seizure-related deaths were witnessed, with two of the brains from these cases showing generalized malformations. Hippocampal anomalies, including a specific combination we termed hippocampal maldevelopment associated with sudden death, were found in almost 50 % (40/83) of the SUDC and undetermined cases in which hippocampal sections were available. Conclusions: This study highlights the key role for the hippocampus, febrile seizures, and sleep in SUDC pathophysiology. It also demonstrates the role of known predisposing conditions such as cardiac channelopathies and infections in causing sudden unexpected death in childhood, and the need for improved ancillary testing and protective strategies in these cases, even when the cause of death is established at autopsy.

Hensleigh, E., & Pritchard, L. M. (2015). Maternal separation increases methamphetamine-induced damage in the striatum in male, but not female rats. *Behavioural Brain Research, 295*, 3-8. Methamphetamine abuse impacts the global economy through costs associated with drug enforcement, emergency room visits, and treatment. Previous research has demonstrated early life stress, such as childhood abuse, increases the likelihood of developing a substance abuse disorder. However, the effects of early life stress on neuronal damage induced by binge

methamphetamine administration are unknown. We aimed to elucidate the effects of early life stress on methamphetamine induced dopamine damage in the striatum. Pups were separated from dams for 3. h per day during the first two weeks of development or 15. min for control. In adulthood, rats received either subcutaneous 0.9% saline or 5.0. mg/kg METH injections every 2. h for a total of four injections. Rectal temperatures were taken before the first injection and 1. h after each subsequent injection. Seven days after treatment, rats were euthanized and striatum was collected for quantification of tyrosine hydroxylase (TH) and dopamine transporters (DAT) content by Western blot. Methamphetamine significantly elevated core body temperature in males and decreased striatal DAT and TH content, and this effect was potentiated by early life stress. Females did not exhibit elevated core body temperatures or changes in DAT or TH in either condition. Results indicate maternal separation increases methamphetamine induced damage, and females are less susceptible to methamphetamine induced damage. © 2014 Elsevier B.V.

Herrinton, L. J., Shorstein, N. H., Paschal, J. F., Liu, L., Contreras, R., Winthrop, K. L., et al. (2015). Comparative effectiveness of antibiotic prophylaxis in cataract surgery. *Ophthalmology,* Purpose: Intracameral injection is an effective method for preventing infection, but no controlled study has been published in the United States. Design: We conducted an observational, longitudinal cohort study to examine the effect of topical and injected antibiotics on risk of endophthalmitis. Participants: We identified 315 246 eligible cataract procedures in 204 515 members of Kaiser Permanente, California, 2005-2012. Methods: The study used information from the membership, medical, pharmacy, and surgical records from the electronic health record. Main Outcome Measures: The adjusted odds ratio (OR) and 95% confidence interval (CI) for the association of antibiotic prophylaxis (route and agent) with risk of endophthalmitis was estimated using logistic regression analysis. Results: We confirmed 215 cases of endophthalmitis (0.07% or 0.7/1000). Posterior capsular rupture was associated with a 3.68-fold increased risk of endophthalmitis (CI, 1.89-7.20). Intracameral antibiotic was more effective than topical agent alone (OR, 0.58; CI, 0.38-0.91). Combining topical gatifloxacin or ofloxacin with intracameral agent was not more effective than using an intracameral agent alone (compared with intracameral only: intracameral plus topical, OR, 1.63; CI, 0.48-5.47). Compared with topical

gatifloxacin, prophylaxis using topical aminoglycoside was ineffective (OR, 1.97; CI, 1.17-3.31). Conclusions: Surgical complication remains a key risk factor for endophthalmitis. Intracameral antibiotic was more effective for preventing post-cataract extraction endophthalmitis than topical antibiotic alone. Topical antibiotic was not shown to add to the effectiveness of an intracameral regimen. © 2015 American Academy of Ophthalmology.

Hoffman, B. D., Gallardo, A. R., & Carlson, K. F. (2015). Unsafe from the start: Serious misuse of car safety seats at newborn discharge. *Journal of Pediatrics,*

Objective: To estimate prevalence of car safety seat (CSS) misuse for newborns on hospital discharge; and to identify potential risk and protective factors for CSS misuse. Study design: We randomly sampled 291 mother-baby dyads from the newborn unit of an academic health center. Participants completed a survey and designated someone (themselves or another caregiver) to position their newborn in the CSS and install the CSS in their vehicle. Certified child passenger safety technicians assessed positioning and installation using nationally standardized criteria. To examine factors associated with CSS misuse, we used logistic regression to compute ORs and 95% CIs. Results: A total of 291 families (81% of those eligible) participated. Nearly all (95%) CSSs were misused, with 1 or more errors in positioning (86%) and/or installation (77%). Serious CSS misuse occurred for 91% of all infants. Frequent misuses included harness and chest clip errors, incorrect recline angle, and seat belt/lower anchor use errors. Families with mothers of color (OR, 6.3; 95% CI, 1.8-21.6), non-English language (OR, 4.9; 95% CI, 1.1-21.2), Medicaid (OR, 10.3; 95% CI, 2.4-44.4), or lower educational level (OR, 4.5; 95% CI, 1.7-12.4) were more likely to misuse CSSs. However, families that worked with a child passenger safety technician before delivery were significantly less likely to misuse their CSSs (OR, 0.1; 95% CI, 0.0-0.4). Conclusion: Nearly all parents of newborn infants misused CSSs. Resources should be devoted to ensuring families with newborns leave the hospital correctly using their CSS. © 2015 Elsevier Inc.

Hoffman, R. S., Vasavada, A. R., Allen, Q. B., Snyder, M. E., Devgan, U., & Braga-Mele, R. (2015). Cataract surgery in the small eye. *Journal of Cataract and Refractive Surgery, 41*(11), 2565-2575.

The surgical management of cataract in the small eye presents the ophthalmic surgeon with numerous challenges. An understanding of the anatomic classification in addition to a thorough preoperative assessment will help individualize each case and enable the surgeon to better prepare for the obstacles that might be encountered during surgery. Small eyes are especially challenging in terms of intraocular lens (IOL) calculations and possible current limitations of available IOL powers, which could necessitate alternative means of achieving emmetropia. Surgical strategies for minimizing complications and maximizing good outcomes can be developed from knowledge of the anatomic differences between various small-eye conditions and the pathologies that may be associated with each. A thorough understanding of the challenges inherent in these cases and the management of intraoperative and postoperative complications will ensure that surgeons approaching the correction of these eyes will achieve the best possible surgical results.

Holliday, E. B., Dieckmann, N. F., McDonald, T. L., Hung, A. Y., Thomas, C. R.,Jr, & Wood, L. J. (2015). Relationship between fatigue, sleep quality and inflammatory cytokines during external beam radiation therapy for prostate cancer: A prospective study. *Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology,*

BACKGROUND AND PURPOSE: Mechanisms of fatigue reported during radiotherapy are poorly defined but may include inflammatory cytokines and/or sleep disturbances. This prospective, longitudinal, phase II study assessed fatigue, sleep, and serum cytokine levels during radiotherapy for early-stage prostate cancer (PCa). MATERIAL AND METHODS: Twenty-eight men undergoing radiotherapy for early-stage PCa wore an Actiwatch Score to record fatigue level, sleep time, onset latency, efficiency and wake after sleep onset. Serum levels of IL-1alpha, IL-1beta, TNF-alpha, IL-6, IL-8, IL-10 and VEGF were measured weekly during radiotherapy. Patient reported quality of life (QOL) metrics were collected before and after treatment. Linear mixed effects models examined trajectories across treatment weeks. RESULTS: Fatigue increased across treatment weeks ($P<.01$), and fatigue was associated with decreased patient-reported QOL. Sleep efficiency increased across treatment weeks (rate of change over time=.29, $P=.03$), and sleep onset latency decreased (rate of change over time=.86, $P=.06$). IL-6 tended to increase during treatment ($P=0.09$), but none of the cytokine levels or sleep variables were significantly

related to fatigue trajectories. CONCLUSIONS: Despite increased sleep efficiency across treatment weeks, fatigue significantly increased. Although IL-6 increased during the course of radiotherapy, cytokines levels were not associated with fatigue scores or sleep disturbance. Further studies are needed to define the mechanisms for fatigue during radiotherapy.

Hoopes, M. J., Angier, H., Gold, R., Bailey, S. R., Huguet, N., Marino, M., et al. (2016). Utilization of community health centers in medicaid expansion and nonexpansion states, 2013-2014. *The Journal of Ambulatory Care Management,*

Using electronic health record data, we examined longitudinal changes in community health center (CHC) visit rates from 2013 through 2014 in Medicaid expansion versus nonexpansion states. Visits from 219 CHCs in 5 expansion states and 4 nonexpansion states were included. Rates were computed using generalized estimating equation Poisson models. Rates increased in expansion state CHCs for new patient, preventive, and limited-service visits (14%, 41%, and 23%, respectively, $P < .01$ for all), whereas these rates remained unchanged in nonexpansion states. One year after ACA Medicaid expansions, CHCs in expansion states saw an influx of new patients and provided increased preventive services.

Hope, E. R., Mhawech-Fauceglia, P., Pejovic, T., Zahn, C. M., Wang, G., Conrads, T. P., et al. (2015). Nestin: A biomarker of aggressive uterine cancers. *Gynecologic Oncology,*

Objective: Evidence of potential prognostic and predictive value for nestin was investigated in well-annotated uterine cancers (UCs). Methods: Nestin expression and previously-published biomarkers were evaluated by immunohistochemistry (IHC) in UC tissue microarrays. Biomarkers were categorized as low vs. high, and nestin was cut at 10% positive staining. Relationship between nestin and clinicopathologic factors, biomarkers and outcome were evaluated using exact/log-rank testing or logistic/Cox modeling. Results: There were 323 eligible cases, 34% had advanced stage disease, 37% had type II disease, and 5% were carcinosarcomas. High nestin, observed in 19% of cases, was more common in advanced vs. early stage disease, type II cancers or uterine carcinosarcoma vs. type I cancers, grade 3 disease, positive lymphovascular space invasion (LVSI) and tumors >. 6. cm (p. <. 0.05). Nestin was inversely correlated with ER, PR and TFF3, and correlated with p53 and IMP3. Women with high vs. low nestin had worse

progression-free survival (PFS) and cancer-specific survival overall, and worse PFS in the subset who received no adjuvant therapy or radiation, or had early stage, type I disease or tumors with both low and high ER, PR, TFF3, PTEN, p53 or IMP3. The relationship between nestin and PFS was independent of stage, LVSI and risk categorization but not type of UC. Conclusions: High nestin was more common in UCs with aggressive features and poor outcome. Nestin may represent a predictive biomarker for treatment selection for patients previously considered to be lower risk and a candidate for no or radiation-based adjuvant therapy, and compliment ER/PR testing. © 2015.

Horikawa, M., Ishikawa, M., Uchida, B. T., Kaufman, J. A., & Farsad, K. (2016). Practical tantalum coating of microspheres for experimental visualization under fluoroscopy and CT. *Journal of Vascular and Interventional Radiology : JVIR, 27*(1), 127-132.

The present report describes a simple technique for tantalum coating of microspheres for visualization by fluoroscopy and computed tomography (CT). Spherical microspheres were soaked with Ta powder under different conditions and microscopically evaluated for Ta-coating quality by assessing bound and unbound Ta. For 100-300-microm Embosphere particles, soaking with 0.05 mL Ta powder for 30 minutes and centrifugation at 500 rpm produced optimal coating. Optimized microspheres were injected in swine renal arteries and assessed by fluoroscopy and micro-CT for the opacification of segmental, arcuate, and interlobular arteries. This practical method can be used for experimental studies with commonly available microspheres.

Hosseinzadeh, P., Marshall, N. M., Chacón, K. N., Yu, Y., Nilges, M. J., New, S. Y., et al. (2016). Design of a single protein that spans the entire 2-V range of physiological redox potentials. *Proceedings of the National Academy of Sciences of the United States of America, 113*(2), 262-267.

The reduction potential (E°′) is a critical parameter in determining the efficiency of most biological and chemical reactions. Biology employs three classes of metalloproteins to cover the majority of the 2-V range of physiological E°′s. An ultimate test of our understanding of E°′ is to find out the minimal number of proteins and their variants that can cover this entire range and the structural features responsible for the extreme E°′. We report herein the design of the protein

azurin to cover a range from +970 mV to -954 mV vs. standard hydrogen electrode (SHE) by mutating only five residues and using two metal ions. Spectroscopic methods have revealed geometric parameters important for the high E°'. The knowledge gained and the resulting water-soluble redox agents with predictable E°'s, in the same scaffold with the same surface properties, will find wide applications in chemical, biochemical, biophysical, and biotechnological fields.

Huang, J. Y., Wang, K., Vermehren-Schmaedick, A., Adelman, J. P., & Cohen, M. S. (2016). PARP6 is a regulator of hippocampal dendritic morphogenesis. *Scientific Reports, 6*, 18512.

Mono-ADP-ribosylation (MARylation) of mammalian proteins was first described as a post-translational modification catalyzed by bacterial toxins. It is now known that endogenous MARylation occurs in mammalian cells and is catalyzed by 11 members of the poly-ADP-ribose polymerase (PARP) family of proteins (17 in humans). The physiological roles of these PARPs remain largely unknown. Here we demonstrate that PARP6, a neuronally enriched PARP that catalyzes MARylation, regulates hippocampal dendrite morphogenesis, a process that is critical for proper neural circuit formation during development. Knockdown of PARP6 significantly decreased dendritic complexity in embryonic rat hippocampal neurons in culture and in vivo. Expression of wild-type PARP6 increased dendritic complexity; conversely, expression of a catalytically inactive PARP6 mutant, or a cysteine-rich domain deletion mutant that has significantly reduced catalytic activity, decreased dendritic complexity. The identification of PARP6 as a regulator of dendrite morphogenesis supports a role for MARylation in neurons during development.

Huang, T., Nickerson, A., Peters, A., & Nan, X. (2015). Quantitative fluorescence nanoscopy for cancer biomedicine. *Biosensing and Nanomedicine VIII, , 9550.*

Cancer is a major health threat worldwide. Options for targeted cancer therapy, however, are often limited, in a large part due to our incomplete understanding of how key processes including oncogenesis and drug response are mediated at the molecular level. New imaging techniques for visualizing biomolecules and their interactions at the nanometer and single molecule scales, collectively named fluorescence nanoscopy, hold the promise to transform biomedical research by providing direct mechanistic insight into cellular processes. We discuss the principles of

quantitative single-molecule localization microscopy (SMLM), a subset of fluorescence nanoscopy, and their applications to cancer biomedicine. In particular, we will examine oncogenesis and drug resistance mediated by mutant Ras, which is associated with ~1/3 of all human cancers but has remained an intractable drug target. At ~20 nm spatial and single-molecule stoichiometric resolutions, SMLM clearly showed that mutant Ras must form dimers to activate its effector pathways and drive oncogenesis. SMLM further showed that the Raf kinase, one of the most important effectors of Ras, also forms dimers upon activation by Ras. Moreover, treatment of cells expressing wild type Raf with Raf inhibitors induces Raf dimer formation in a manner dependent on Ras dimerization. Together, these data suggest that Ras dimers mediate oncogenesis and drug resistance in tumors with hyperactive Ras and can potentially be targeted for cancer therapy. We also discuss recent advances in SMLM that enable simultaneous imaging of multiple biomolecules and their interactions at the nanoscale. Our work demonstrates the power of quantitative SMLM in cancer biomedicine.

Huckans, M., Fuller, B. E., Chalker, A. L., Adams, M., & Loftis, J. M. (2015). Plasma inflammatory factors are associated with anxiety, depression, and cognitive problems in adults with and without methamphetamine dependence: An exploratory protein array study. *Frontiers in Psychiatry, 6*, 178.

OBJECTIVES: It is hypothesized that immune factors influence addictive behaviors and contribute to relapse. The primary study objectives were to (1) compare neuropsychiatric symptoms across adults with active methamphetamine (MA) dependence, in early remission from MA dependence, and with no history of substance dependence, (2) determine whether active or recent MA dependence affects the expression of immune factors, and (3) evaluate the association between immune factor levels and neuropsychiatric symptoms. METHODS: A cross-sectional study was conducted using between group comparisons and regression analyses to investigate associations among variables. Eighty-four adults were recruited into control (CTL) (n = 31), MA-active (n = 17), or MA-remission (n = 36) groups. Participants completed self-report measures of anxiety, depression, and memory complaints and objective tests of attention and executive function. Blood samples were collected, and a panel of immune factors was measured using multiplex technology. RESULTS: Relative to CTLs, MA-dependent adults evidenced greater anxiety and

depression during active use ($p < 0.001$) and remission ($p < 0.007$), and more attention, memory, and executive problems during remission ($p < 0.01$) but not active dependence. Regression analyses identified 10 immune factors (putatively associated with cytokine-cytokine receptor interactions) associated with anxiety, depression, and memory problems. CONCLUSION: While psychiatric symptoms are present during active MA dependence and remission, at least some cognitive difficulties emerge only during remission. Altered expression of a network of immune factors contributes to neuropsychiatric symptom severity.

Hullar, T. E. (2016). Getting the most from cochlear implants. *JAMA Otolaryngology-- Head & Neck Surgery,*

Hunter, L. L., Keefe, D. H., Feeney, M. P., Fitzpatrick, D. F., & Lin, L. (2015). Longitudinal development of wideband reflectance tympanometry in normal and at-risk infants. *Hearing Research,*

Purpose: The goals of this study were to measure normal characteristics of ambient and tympanometric wideband acoustic reflectance, which was parameterized by absorbance and group delay, in newborns cared for in well-baby and Neonatal Intensive Care Unit (NICU) nurseries, and to characterize the normal development of reflectance over the first year after birth in a group of infants with clinically normal hearing status followed longitudinally from birth to one year of age. Methods: Infants were recruited from a well-baby and NICU nursery, passed newborn otoacoustic emissions (OAE) and automated auditory brainstem response (ABR) tests as well as follow-up diagnostic ABR and audiometry. They were tested longitudinally for up to one year using a wideband middle ear acoustic test battery consisting of tympanometry and ambient-pressure tests. Results were analyzed for ambient reflectance across frequency and tympanometric reflectance across frequency and pressure. Results: Wideband absorbance and group delay showed large effects of age in the first 6 months. Immature absorbance and group delay patterns were apparent in the low frequencies at birth and one month, but changed substantially to a more adult-like pattern by age 6 months for both ambient and tympanometric variables. Area and length of the ear canal estimated acoustically increased up to age 1 year. Effects of race (African American and others compared to Caucasian) were found in combination

with age effects. Mean and confidence intervals are provided for use as a normative longitudinal database for newborns and infants up to one year of age, for both well-baby and NICU infants. © 2015.

Hwang, T. S., Gao, S. S., Liu, L., Lauer, A. K., Bailey, S. T., Flaxel, C. J., et al. (2016). Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmology,* , 1-7.

Importance: Macular ischemia is a key feature of diabetic retinopathy (DR). Quantification of macular ischemia has potential as a biomarker for DR. Objective: To assess the feasibility of automated quantification of capillary nonperfusion as a potential sign of macular ischemia using optical coherence tomography (OCT) angiography. Design, Setting, and Participants: An observational study conducted in a tertiary, subspecialty, academic practice evaluated macular nonperfusion with 6 x 6-mm OCT angiography obtained with commercially available 70-kHz OCT and fluorescein angiography (FA). The study was conducted from January 22 to September 18, 2014. Data analysis was performed from October 1, 2014, to April 7, 2015. Participants included 12 individuals with normal vision serving as controls and 12 patients with various levels of DR. Main Outcomes and Measures: Preplanned primary measures were parafoveal and perifoveal vessel density, total avascular area, and foveal avascular zone as detected with 6 x 6-mm OCT angiography and analyzed using an automated algorithm. Secondary measures included the agreement of the avascular area between the OCT angiogram and FA. Results: Compared with the 12 healthy controls (11 women; mean [SD] age, 54.2 [14.2] years), the 12 participants with DR (4 women; mean [SD] age, 55.1 [12.1] years) had reduced parafoveal and perifoveal vessel density by 12.6% (95% CI, 7.7%-17.5%; P < .001) and 10.4% (95% CI, 6.8%-14.1%; P < .001), respectively. Total avascular area and foveal avascular zone area were greater in eyes with DR by 0.82 mm2 (95% CI, 0.65-0.99 mm2; P = .02) and 0.16 mm2 (95% CI, 0.05-0.28 mm2; P < .001). The agreement between the vascular areas in the OCT angiogram and FA had a kappa value of 0.45 (95% CI, 0.21-0.70; P < .001). Total avascular area in the central 5.5-mm-diameter area distinguished eyes with DR from control eyes with 100% sensitivity and specificity. Conclusions and Relevance: Avascular area analysis with an automated algorithm using OCT angiography, although not equivalent to FA, detected DR reliably in this small pilot study. Further

study is necessary to determine the usefulness of the automated quantification in clinical practice.

Hyun, H. -., Salehi, S., & Ferracane, J. L. (2015). Biofilm formation affects surface properties of novel bioactive glass-containing composites. *Dental Materials, 31*(12), 1599-1608.

Objectives This study investigated the effects of bacterial biofilm on the surface properties of novel bioactive glass (BAG)-containing composites of different initial surface roughness. Methods BAG (65 mol% Si; 4% P; 31% Ca) and BAG-F (61% Si; 31% Ca; 4% P; 3% F; 1% B) were synthesized by the sol-gel method and micronized (size ~0.1-10 μm). Composites with 72 wt% total filler load were prepared by replacing 15% of the silanized Sr glass with BAG, BAG-F, or silanized silica. Specimens (n = 10/group) were light-cured and divided into 4 subgroups of different surface roughness by wet polishing with 600 and then up to 1200, 2400, or 4000 grit SiC. Surface roughness (SR), gloss, and Knoop microhardness were measured before and after incubating in media with or without a Streptococcus mutans (UA 159) biofilm for 2 weeks. Results were analyzed with ANOVA/Tukey's test (α = 0.05). Results The SR of the BAG-containing composites with the smoothest surfaces (2400/4000 grit) increased in media or bacteria; the SR of the roughest composites (600 grit) decreased. The gloss of the smoothest BAG-containing composites decreased in bacteria and media-only, but more in media-alone. The microhardness of all of the composites decreased with exposure to media or bacteria, with BAG-containing composites affected more than the control. Significance Exposure to bacterial biofilm and its media produced enhanced roughness and reduced gloss and surface microhardness of highly polished dental composites containing a bioactive glass additive, which could affect further biofilm formation, as well as the esthetics, of restorations made from such a material.

Ianchulev, T., Litoff, D., Ellinger, D., Stiverson, K., & Packer, M. (2016). Office-based cataract surgery: Population health outcomes study of more than 21 000 cases in the united states. *Ophthalmology,*

PURPOSE: To identify safety and effectiveness outcomes of office-based cataract surgery. Each year, approximately 3.7 million cataract surgeries in the United States are performed in

Ambulatory Surgery Center (ASC) and Hospital Outpatient Department (HOPD) locations. Medicare in July 2015 published a solicitation for expert opinion on reimbursing office-based cataract surgery. DESIGN: Large-scale, retrospective, consecutive case series of cataract surgeries performed in Minor Procedure Rooms (MPRs) of a large US integrated healthcare center. PARTICIPANTS: More than 13 500 patients undergoing elective office-based cataract surgery. METHODS: Phacoemulsification cataract surgery performed in MPRs of Kaiser Permanente Colorado from 2011 to 2014. MAIN OUTCOME MEASURES: Postoperative visual acuity and intraoperative and postoperative adverse events (AEs). RESULTS: Office-based cataract surgery was completed in 21 501 eyes (13 507 patients, age 72.6+/-9.6 years). Phacoemulsification was performed in 99.9% of cases, and manual extracapsular extraction was performed in 0.1% of cases. Systemic comorbidities included hypertension (53.5%), diabetes (22.3%), and chronic obstructive pulmonary disease (9.4%). Postoperative mean best-corrected visual acuity measured 0.14+/-0.26 logarithm of the minimum angle of resolution units. Intraoperative ocular AEs included 119 (0.55%) cases of capsular tear and 73 (0.34%) cases of vitreous loss. Postoperative AEs included iritis (n = 330, 1.53%), corneal edema (n = 110, 0.53%), and retinal tear or detachment (n = 30, 0.14%). No endophthalmitis was reported. Second surgeries were performed in 0.70% of treated eyes within 6 months. There were no life- or vision-threatening intraoperative or perioperative AEs. CONCLUSIONS: This is the largest US study to investigate the safety and effectiveness of office-based cataract surgery performed in MPRs. Office-based efficacy outcomes were consistently excellent, with a safety profile expected of minimally invasive cataract procedures performed in ASCs and HOPDs.

Imber, B. S., Braunstein, S. E., Wu, F. Y., Nabavizadeh, N., Boehling, N., Weinberg, V. K., et al. (2016). Clinical outcome and prognostic factors for central neurocytoma: Twenty year institutional experience. *Journal of Neuro-Oncology, 126*(1), 193-200.

Central neurocytomas are uncommon intraventricular neoplasms whose optimal management remains controversial due to their rarity. We assessed outcomes for a historical cohort of neurocytoma patients and evaluated effects of tumor atypia, size, resection extent, and adjuvant radiotherapy. Progression-free survival (PFS) was measured by Kaplan–Meier and Cox proportional hazards methods. A total of 28 patients (15 males, 13 females) were treated

between 1995 and 2014, with a median age at diagnosis of 26 years (range 5–61). Median follow-up was 62.2 months and 3 patients were lost to follow-up postoperatively. Thirteen patients experienced recurrent/progressive disease and 2-year PFS was 75 % (95 % CI 53–88 %). Two-year PFS was 48 % for MIB-1 labeling >4 % versus 90 % for ≤4 % (HR 5.4, CI 2.2–27.8, p = 0.0026). Nine patients (32 %) had gross total resections (GTR) and 19 (68 %) had subtotal resections (STR). PFS for >80 % resection was 83 versus 67 % for ≤80 % resection (HR 0.67, CI 0.23–2.0, p = 0.47). Three STR patients (16 %) received adjuvant radiation which significantly improved overall PFS (p = 0.049). Estimated 5-year PFS was 67 % for STR with radiotherapy versus 53 % for STR without radiotherapy. Salvage therapy regimens were diverse and resulted in stable disease for 54 % of patients and additional progression for 38 %. Two patients with neuropathology-confirmed atypical neurocytomas died at 4.3 and 113.4 months after initial surgery. For central neurocytomas, MIB-1 labeling index >4 % is predictive of poorer outcome and our data suggest that adjuvant radiotherapy after STR may improve PFS. Most patients requiring salvage therapy will be stabilized and multiple modalities can be effectively utilized.

Ingelse, K., & Messecar, D. (2015). Rural women veterans' use and perception of mental health services. *Archives of Psychiatric Nursing,*

While the total number of veterans in the U.S. is decreasing overall, the number of women veterans is significantly increasing. There are numerous barriers which keep women veterans from accessing mental health care. One barrier which can impact receiving care is living in a rural area. Veterans in rural areas have access to fewer mental health services than do urban residing veterans, and women veterans in general have less access to mental health care than do their male colleagues. Little is known about rural women veterans and their mental health service needs. Women, who have served in the military, have unique problems related to their service compared to their male colleagues including higher rates of post-traumatic stress disorder (PTSD) and military sexual trauma (MST). This qualitative study investigated use of and barriers to receiving mental health care for rural women veterans. In-depth interviews were conducted with ten women veterans who have reported experiencing problems with either MST, PTSD, or combat trauma. All ten women had utilized mental health services during active-duty military service,

and post service, in Veterans Administration (VA) community based-outpatient clinics. Several recurring themes in the women's experience were identified. For all of the women interviewed, a sentinel precipitating event led to seeking mental health services. These precipitating events included episodes of chronic sexual harassment and ridicule, traumatic sexual assaults, and difficult combat experiences. Efforts to report mistreatment were unsuccessful or met with punishment. All the women interviewed reported that they would not have sought services without the help of a supportive peer who encouraged seeking care. Barriers to seeking care included feeling like they were not really a combat veteran (in spite of serving in a combat unit in Iraq); feeling stigmatized by providers and other military personnel, being treated as crazy; and a lack of interest from those providing care in hearing their stories. This study may generate positive social change by helping providers approach women veterans in a way that is sympathetic to their experiences.

Izumi, S., & Van Son, C. (2016). "I didn't know he was dying": Missed opportunities for making end-of-life care decisions for older family members. *Journal of Hospice and Palliative Nursing, 18*(1), 74-81.

Research is limited on end-of-life care decision-making for older adults with chronic conditions whose end-of-life trajectory is difficult to predict because of their complex and frail condition. Semistructured interviews were conducted with family members of 22 deceased older adults to explore their experiences with end-of-life decision-makingwith/for their loved ones. Participants did not identify a specific time they made an end-of-life care decision as they did not know the older adult was at the end of life, health care providers did not ask them to make a decision, or they had to make forced decisions, and subsequently they experienced regret about the end-of-life care their family member received. End-of-life care decisions were dependent on the awareness of approaching death by participants, their loved ones, and health care providers. Health care providers being aware of the possibility of approaching death and assisting family members to make decisions that would honor the older adult's preference by explaining possible care options and what each care options would mean to them are key to providing quality end-of-life care for these individuals.

Janowsky, A., Tosh, D. K., Eshleman, A. J., & Jacobson, K. A. (2016). Rigid adenine nucleoside derivatives as novel modulators of the human sodium symporters for dopamine and other neurotransmitters. *The Journal of Pharmacology and Experimental Therapeutics,*

Thirty two congeneric rigid adenine nucleoside derivatives containing a (N)-methanocarba ribose substitution and a 2-arylethynyl group either enhanced (up to 760% of control) or inhibited [125I]RTI-55 binding at the human dopamine (DA) transporter (DAT) and inhibited DA uptake. Several nucleosides also enhanced [3H]mazindol binding to DAT. The combination of binding enhancement and functional inhibition suggests possible allosteric interaction with the tropanes. The structure-activity relationship (SAR) of this novel class of DAT ligands was explored: small N6-substition (methyl or ethyl) was favored, while the N1 of the adenine ring was essential. Effective terminal aryl groups include thien-2-yl (9 and 16, with EC50s in [125I]RTI-55 binding enhancement of 35.1 and 9.1 nM, respectively) and 3,4-difluorophenyl (as in the most potent DA uptake inhibitor 6 with IC50 of 92 nM, 3-fold more potent than cocaine), but not nitrogen heterocycles. Several compounds inhibited or enhanced binding at NET and SERT and inhibited function in the micromolar range. Truncation at the 4'-position in 23 allowed for weak inhibition of the SERT. We have not yet eliminated adenosine receptor affinity from this class of DAT modulators, but we identified modifications that remove DAT inhibition as an off-target effect of potent adenosine receptor agonists. Thus, we have identified a new class of allosteric DAT ligands, rigidified adenosine derivatives, and explored their initial structural requirements. They display a very atypical pharmacological profile, i.e. either enhancement by increasing affinity, or inhibition of radioligand binding at DAT, and in some cases NET and SERT, and inhibition of neurotransmitter uptake.

Jasti, J., Fernandez, A. R., Schmidt, T. A., & Lerner, E. B. (2016). EMS provider attitudes and perceptions of enrolling patients without consent in prehospital emergency research. *Prehospital Emergency Care, 20*(1), 22-27.

The purpose of this study was to evaluate the attitudes and opinions of a broad population of EMS providers on enrolling patients in research without consent. A survey was conducted in 2010 of all EMS providers who participated in the National Registry of Emergency Medical Technicians (NREMT) reregistration process, which included half of all registered providers. Each

reregistration packet included our optional survey, which had nine 6-point Likert scale questions concerning their opinion of research studies without consent as well as 8 demographic questions. Responses were collapsed to agree and disagree and then analyzed using descriptive statistics with 99% confidence intervals. A total of 65,993 EMS providers received the survey and 23,832 (36%) participated. Most respondents agreed (98.4%, 99%CI: 98.2-98.6) that EMS research is important, but only 30.9% (99%CI: 30.1-31.6) agreed with enrolling patients without their consent when it is important to learn about a new treatment. Only 46.6% (99%Cl: 45.7-47.4) were personally willing to be enrolled in a study without their consent. A majority (68.5% [99%Cl: 67.7-69.3]) of respondents believed that EMS providers should have the individual right to refuse to enroll patients in EMS research. While the majority of respondents agreed that EMS research is important, considerably less agree with enrolling patients without consent and less than half would be willing to be enrolled in a study without their consent. Prior to starting an Exception from Informed Consent (EFIC) study, researchers should discuss with EMS providers their perceptions of enrolling patients without consent and address their concerns. © 2016 National Association of EMS Physicians.

Jayaram, H., Cepurna, W. O., Johnson, E. C., & Morrison, J. C. (2015). MicroRNA expression in the glaucomatous retina. *Investigative Ophthalmology and Visual Science, 56*(13), 7971-7982. PURPOSE. MicroRNAs are small, endogenous noncoding RNAs that modulate posttranscrip- tional gene expression. Although the contribution of microRNAs to the pathogenesis of glaucomatous damage is unknown, supporting evidence from central nervous system (CNS) research suggests they may play a role. It was therefore hypothesized that microRNAs known to be altered in CNS injury are also altered in experimental glaucoma. METHODS. Intraocular pressure (IOP) was elevated in rats by unilateral injection of hypertonic saline and IOP monitored for 5 weeks. After rats were killed, retrobulbar optic nerve sections were graded for damage. MicroRNA was extracted from whole retinae of eyes with advanced nerve damage (n = 8) and from normal, noninjected control eyes (n = 8). Quantitative PCRs were performed using a panel of 17 microRNAs, reported from CNS research to be implicated in mechanisms also linked to glaucomatous damage. Computationally and experimentally derived gene targets were identified for the differentially expressed microRNAs. These were then integrated with existing gene array

data. Functional interpretation was performed using the Molecular Signatures Database and DAVID Functional Annotation Clustering. RESULTS. Eight microRNAs were significantly downregulated in glaucomatous retinae compared with controls (miR-181c, miR-497, miR-204, let-7a, miR-29b, miR-16, miR106b, and miR-25); miR-27a was significantly upregulated. Enrichment of targets associated with extracellular matrix/cell proliferation, immune system, and regulation of apoptosis were observed. Cholesterol homeostasis and mTORC-1 pathways showed reduced expression. CONCLUSIONS. MicroRNAs are differentially expressed in retinae of eyes with advanced glaucomatous damage compared with normal controls. Integrating microRNA with gene expression data may improve understanding of the complex biological responses produced by chronically elevated IOP.

Jim, H. S., Lin, H. Y., Tyrer, J. P., Lawrenson, K., Dennis, J., Chornokur, G., et al. (2015). Common genetic variation in circadian rhythm genes and risk of epithelial ovarian cancer (EOC). *Journal of Genetics and Genome Research, 2*(2), 017. Epub 2015 Sep 15.

Disruption in circadian gene expression, whether due to genetic variation or environmental factors (e.g., light at night, shiftwork), is associated with increased incidence of breast, prostate, gastrointestinal and hematologic cancers and gliomas. Circadian genes are highly expressed in the ovaries where they regulate ovulation; circadian disruption is associated with several ovarian cancer risk factors (e.g., endometriosis). However, no studies have examined variation in germline circadian genes as predictors of ovarian cancer risk and invasiveness. The goal of the current study was to examine single nucleotide polymorphisms (SNPs) in circadian genes BMAL1, CRY2, CSNK1E, NPAS2, PER3, REV1 and TIMELESS and downstream transcription factors KLF10 and SENP3 as predictors of risk of epithelial ovarian cancer (EOC) and histopathologic subtypes. The study included a test set of 3,761 EOC cases and 2,722 controls and a validation set of 44,308 samples including 18,174 (10,316 serous) cases and 26,134 controls from 43 studies participating in the Ovarian Cancer Association Consortium (OCAC). Analysis of genotype data from 36 genotyped SNPs and 4600 imputed SNPs indicated that the most significant association was rs117104877 in BMAL1 (OR = 0.79, 95% CI = 0.68-0.90, p = 5.59 x 10-4]. Functional analysis revealed a significant down regulation of BMAL1 expression following cMYC

overexpression and increasing transformation in ovarian surface epithelial (OSE) cells as well as alternative splicing of BMAL1 exons in ovarian and granulosa cells. These results suggest that variation in circadian genes, and specifically BMAL1, may be associated with risk of ovarian cancer, likely through disruption of hormonal pathways.

Jimison, H. B., Hagler, S., Kurillo, G., Bajcsy, R., & Pavel, M. (2015). Remote health coaching for interactive exercise with older adults in a home environment. *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2015, , 2015-November.* pp. 5485-5488.

Optimal health coaching interventions are tailored to individuals' needs, preferences, motivations, barriers, timing, and readiness to change. Technology approaches are useful in both monitoring a user's adherence to their behavior change goals and also in providing just-in-time feedback and coaching messages. User models that incorporate dynamically varying behavior change variables with algorithms that trigger tailored messages provide a framework for making health interventions more effective. These principles are applied in the described system for assisting older adults in meeting their physical exercise goals with a tailored interactive video system with just-in-time feedback and encouragement. © 2015 IEEE.

Johnson, E. A., Zubair, M. M., Armsby, L. R., Burch, G. H., Good, M. K., Lasarev, M. R., et al. (2016). Surgical quality predicts length of stay in patients with congenital heart disease. *Pediatric Cardiology,*

Historically, the primary marker of quality for congenital cardiac surgery has been postoperative mortality. The purpose of this study was to determine whether additional markers (10 surgical metrics) independently predict length of stay (LOS), thereby providing specific targets for quality improvement. Ten metrics (unplanned ECMO, unplanned cardiac catheterization, revision of primary repair, delayed closure, mediastinitis, reexploration for bleeding, complete heart block, vocal cord paralysis, diaphragm paralysis, and change in preoperative diagnosis) were defined in 2008 and subsequently collected from 1024 consecutive index congenital cardiac cases, yielding 990 cases. Four patient characteristics and 22 case characteristics were used for risk adjustment. Univariate and multivariable analyses were used to determine independent associations between

each metric and postoperative LOS. Increased LOS was independently associated with revision of the primary repair ($p = 0.014$), postoperative complete heart block requiring a permanent pacemaker ($p = 0.001$), diaphragm paralysis requiring plication ($p < 0.001$), and unplanned postoperative cardiac catheterization ($p < 0.001$). Compared with patients without each metric, LOS was 1.6 (95 % CI 1.1-2.2, $p = 0.014$), 1.7 (95 % CI 1.2-2.3, $p = 0.001$), 1.8 (95 % CI 1.4-2.3, $p < 0.001$), and 2.0 (95 % CI 1.7-2.4, $p < 0.001$) times as long, respectively. These effects equated to an additional 4.5-7.8 days in hospital, depending on the metric. The other 6 metrics were not independently associated with increased LOS. The quality of surgery during repair of congenital heart disease affects outcomes. Reducing the incidence of these 4 specific surgical metrics may significantly decrease LOS in this population.

Johnson, L. A., Zuloaga, K. L., Kugelman, T. L., Mader, K. S., Morré, J. T., Zuloaga, D. G., et al. (2015). Amelioration of metabolic syndrome-associated cognitive impairments in mice via a reduction in dietary fat content or infusion of non-diabetic plasma. *Ebiomedicine,*

Obesity, metabolic syndrome (MetS) and type 2 diabetes (T2D) are associated with decreased cognitive function. While weight loss and T2D remission result in improvements in metabolism and vascular function, it is less clear if these benefits extend to cognitive performance. Here, we highlight the malleable nature of MetS-associated cognitive dysfunction using a mouse model of high fat diet (HFD)-induced MetS. While learning and memory was generally unaffected in mice with type 1 diabetes (T1D), multiple cognitive impairments were associated with MetS, including deficits in novel object recognition, cued fear memory, and spatial learning and memory. However, a brief reduction in dietary fat content in chronic HFD-fed mice led to a complete rescue of cognitive function. Cerebral blood volume (CBV), a measure of vascular perfusion, was decreased during MetS, was associated with long term memory, and recovered following the intervention. Finally, repeated infusion of plasma collected from age-matched, low fat diet-fed mice improved memory in HFD mice, and was associated with a distinct metabolic profile. Thus, the cognitive dysfunction accompanying MetS appears to be amenable to treatment, related to cerebrovascular function, and mitigated by systemic factors.

Johnson, R. C., Kim, J., Natkunam, Y., Sundram, U., Freud, A. G., Gammon, B., et al. (2016). Myeloid cell nuclear differentiation antigen (MNDA) expression distinguishes extramedullary presentations of myeloid leukemia from blastic plasmacytoid dendritic cell neoplasm. *The American Journal of Surgical Pathology,*

Myeloid neoplasms constitute one of the most common malignancies in adults. In most cases these proliferations initially manifest in the blood and marrow; however, extramedullary involvement may precede blood or marrow involvement in a subset of cases, making a definitive diagnosis challenging by morphologic and immunohistochemical assessment alone. Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive entity that frequently presents in extramedullary sites and can show morphologic and immunophenotypic overlap with myeloid neoplasms. Given that BPDCN and myeloid neoplasms may both initially present in extramedullary sites and that novel targeted therapies may be developed that exploit the unique molecular signature of BPDCN, new immunophenotypic markers that can reliably separate myeloid neoplasms from BPDCN are desirable. We evaluated the utility of myeloid cell nuclear differentiation antigen (MNDA) expression in a series of extramedullary myeloid leukemias (EMLs) and BPDCN. Forty biopsies containing EML and 19 biopsies containing BPDCN were studied by MNDA immunohistochemistry. The majority of myeloid neoplasms showed nuclear expression of MNDA (65%). In contrast, all cases of BPDCN lacked MNDA expression. These findings show that MNDA is expressed in the majority of EMLs and support the inclusion of MNDA immunohistochemistry in the diagnostic evaluation of blastic hematopoietic infiltrates, particularly when the differential diagnosis is between myeloid leukemia and BPDCN.

Jonker, S. S., & Louey, S. (2016). Endocrine and other physiologic modulators of perinatal cardiomyocyte endowment. *Journal of Endocrinology, 228*(1), R1-R18.

Immature contractile cardiomyocytes proliferate to rapidly increase cell number, establishing cardiomyocyte endowment in the perinatal period. Developmental changes in cellular maturation, size and attrition further contribute to cardiac anatomy. These physiological processes occur concomitant with a changing hormonal environment as the fetus prepares itself for the transition to extrauterine life. There are complex interactions between endocrine, hemodynamic and nutritional regulators of cardiac development. Birth has been long assumed to be the trigger for

major differences between the fetal and postnatal cardiomyocyte growth patterns, but investigations in normally growing sheep and rodents suggest this may not be entirely true; in sheep, these differences are initiated before birth, while in rodents they occur after birth. The aim of this review is to draw together our understanding of the temporal regulation of these signals and cardiomyocyte responses relative to birth. Further, we consider how these dynamics are altered in stressed and suboptimal intrauterine environments. © 2016 Society for Endocrinology.

Ju, H., & Hart, R. A. (2015). Hidden blood loss in anterior lumbar interbody fusion (ALIF) surgery. *Orthopaedics and Traumatology: Surgery and Research,*

Background: A retrospective study was performed to determine the factors affecting the total perioperative blood loss during anterior lumbar interbody fusion (ALIF). Measurements of intraoperative blood loss underestimate the true blood loss during surgery. Our research project was to examine the hidden blood loss in lumbar spine surgery. Hidden blood loss in elective knee and hip replacement surgeries range between 100% and 30%. Hidden blood loss was about 40% in posterior spine surgery. Methods: The factors analyzed included gender, body mass index (BMI), duration of surgery, type of surgery, aspiration, and number of fusion levels. Estimated blood loss (EBL) was obtained from the clinical records of patients as the blood collected from suctioning and the cumulative weight of the saturated sponges. Actual blood loss (ABL) was calculated from the estimated blood volume and hemoglobin level of patients. Hidden blood loss was calculated as the difference between ABL and EBL. Results: Seventy-eight consecutive patients who underwent ALIF were reviewed. The average values (mean. ±. SD) for EBL and ABL were 700.1. ±. 562.3. mL and 1150.6. ±. 770.0. mL, respectively (P = 0.001, Student's t-test). The hidden blood loss averaged 39.2% of the ABL. According to linear regression analysis, surgical duration, type of surgery, and the inclusion of the L4/5 level were independent factors contributing to the ABL (P <. 0.05), whereas BMI and gender did not correlate with ABL or EBL. Conclusions: ALIF is associated with substantial perioperative hidden blood loss. Length of surgery, type of surgery, and the inclusion of L4/5 in the procedure are significant risk factors for increased blood loss. Level of evidence: Level IV: retrospective or historical series. © 2015 Elsevier Masson SAS.

Kahi, C. J., & Lieberman, D. (2016). Family history of colorectal adenomas: Taking the methodological bull by the horns. *Gastroenterology,*

Kaneshiro, B., Edelman, A., Dash, C., Pandhare, J., Soli, F. M., & Jensen, J. T. (2016). Effect of oral contraceptives and doxycycline on endometrial MMP-2 and MMP-9 activity. *Contraception, 93*(1), 65-69.

Objectives To describe the effect of combined oral contraceptives (COCs) on matrix metalloproteinases MMP-2 and MMP-9 activity and compare MMP activity in women taking a COC with or without doxycycline. Study design Subjects (n= 20) underwent endometrial biopsies (1) in the late luteal phase of a baseline cycle prior to initiating COCs, (2) on days 19-21 while taking COCs in a standard 28-day cycle (7-day hormone-free interval) and (3) on days 26-28 while taking active COCs continuously for a 28-day cycle. During the continuous COC cycle, they were randomized to receive daily subantimicrobial dose doxycycline 40 mg or placebo. Results Compared to baseline, COC treatment increased MMP-2 (p<.001) and MMP-9 (p<.001). MMP activity was lower in subjects taking a COC with doxycycline compared to those receiving placebo although only significantly lower for MMP-2 latent form (p=.002). Conclusions Unscheduled bleeding with COCs may be the result of increased endometrial MMPs. Sample size limitations prevent us from determining how doxycycline affects MMP activity in COC users. © 2016 Published by Elsevier Inc.

Kaplan, M. S., Huguet, N., McFarland, B. H., Caetano, R., Conner, K. R., Nolte, K. B., et al. (2016). Heavy alcohol use among suicide decedents: Differences in risk across racial-ethnic groups. *Psychiatric Services (Washington, D.C.),* , appips201500494.

Karam, C. (2016). Bright tongue sign in pompe disease. *Neurology, 86*(4), 401.

Karna, S. K., Rohit, M. K., & Wanchu, A. (2015). Right ventricular thickness as predictor of global myocardial performance in systemic sclerosis: A doppler tissue imaging study. *Indian Heart Journal, 67*(6), 521-528.

Background Cardiopulmonary involvement in systemic sclerosis (SSc) is a poor prognostic factor, due to pulmonary hypertension and right ventricular dysfunction. We assessed the

echocardiographic parameters of right ventricular (RV) function in SSc and correlated echocardiographic findings to clinical features of the disease. Methods Thirty patients with SSc (cases) and 30 healthy, age-matched subjects (controls) were studied. Echocardiography, including tissue Doppler imaging, was used to evaluate cardiac function. Results Pulmonary hypertension could be documented in only 5 cases by Doppler echo, using Bernoulli principle. RV diastolic function was significantly deranged in cases. RV systolic function and left ventricle (LV) diastolic function were also significantly deranged in the cases. RV thickness was increased in patients with SSc. There were no significant differences in the echocardiographic variables between diffuse and limited subtypes of SSc. Myocardial performance index (MPI) of both ventricles were increased in cases. We could demonstrate RV thickness as the single most important predictor of MPI of both ventricles with sensitivity of 82% and specificity of 72% for RV-MPI and 63% for LV-MPI. Diastolic function was not found to be affected by disease duration or Rodnan skin score. Conclusion Patients with SSc exhibit abnormal RV and LV diastolic functions as well as abnormal RV systolic function. RV wall thickness was found to be simple and the single best predictor of global myocardial performance. RV dysfunction may be a response to intermittent pulmonary arterial hypertension, lung parenchymal involvement, or secondary to LV diastolic dysfunction in SSc. © 2015 Cardiological Society of India.

Kärnä, T., & Baptista, A. M. (2016). Evaluation of a long-term hindcast simulation for the columbia river estuary. *Ocean Modelling, 99*, 1-14.

In order to simulate the biogeochemical function of estuaries across the land-ocean continuum, circulation models must represent a cascade of complex physical processes spanning several spatial and temporal scales. Furthermore, governing physical processes tend to vary under different flow regimes, in response to external forcings. Model validation must therefore cover all relevant flow regimes and span sufficiently long time to represent transient and slowly-varying phenomena. We focus in a multi-year hindcast simulation of the Columbia River estuary - a mesotidal, river-dominated estuary that is also influenced by coastal upwelling in an Eastern Boundary Current system. Model skill is assessed against long-term observational time series, covering the lower estuary (for salinity) as well as most of the tidal river (for water temperature and elevation). In addition, high-resolution profiles of velocity and salinity are used to study salt

transport mechanisms at a single station. Results indicate that the model captures the estuarine dynamics of the system, but the skill depends on the flow regime: In general the model performs far better during spring tides (i.e., under partially mixed or time-dependent salt wedge regimes) than under neap tides (i.e., salt wedge and strongly stratified regimes). While the model accurately represents tidal salt transport mechanisms, it tends to underestimate gravitational transport which becomes more important under neap tide conditions. Furthermore, the skill decreases during high river discharge periods, because the model has difficulty capturing the extremely strong stratification characteristic to those periods. © 2016 The Authors.

Kea, B., Fu, R., Lowe, R. A., & Sun, B. C. (2016). Interpreting the national hospital ambulatory medical care survey: United states emergency department opioid prescribing, 2006-2010. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine,* OBJECTIVES: Prescription opioid overdoses are a leading cause of death in the United States. Emergency departments (EDs) are potentially high-risk environments for doctor shopping and diversion. The hypothesis was that opioid prescribing rates from the ED have increased over time. METHODS: The authors analyzed data on ED discharges from the 2006 through 2010 NHAMCS, a probability sample of all U.S. EDs. The outcome was documentation of an opioid prescription on discharge. The primary independent predictor was time. Covariates included severity of pain, a pain-related discharge diagnosis, age, sex, race, payer, hospital ownership, and geographic location of hospital. Up to three discharge diagnoses were available in NHAMCS to identify "pain-related" (e.g., back pain, fracture, dental/jaw pain, nephrolithiasis) ED visits. Multivariate logistic regression was performed to assess the independent associations between opioid prescribing and predictors. All analyses incorporated NHAMCS survey weights, and all results are presented as national estimates. RESULTS: Opioids were prescribed for 18.7% (95% confidence interval = 17.7% to 19.7%) of all ED discharges, representing 18.8 million prescriptions per year. There were no significant temporal trends in opioid prescribing overall (adjusted p = 0.93). Pain-related discharge diagnoses that received the top three highest proportion of opioids prescriptions included nephrolithiasis (62.1%), neck pain (51.6%), and dental/jaw pain (49.7%). A pain-related discharge diagnosis, non-Hispanic white race, older age, male sex, uninsured status, and Western region were positively associated with opioid prescribing

($p < 0.05$). CONCLUSIONS: No temporal trend toward increased prescribing from 2006 to 2012 was found. These results suggest that problems with opioid overprescribing are multifactorial and not solely rooted in the ED.

Kiage, J. N., Sampson, U. K. A., Lipworth, L., Fazio, S., Mensah, G. A., Yu, Q., et al. (2016). Polyunsaturated fat intake and mortality in non-statin users, is there an independent relationship? the authors reply. *Nutrition, Metabolism and Cardiovascular Diseases, 26*(1), 78-79.

Kim, H., Hartung, D. M., Jacob, R. L., McCarty, D., & McConnell, K. J. (2016). The concentration of opioid prescriptions by providers and among patients in the oregon medicaid program. *Psychiatric Services (Washington, D.C.),* , appips201500116.

OBJECTIVE: This study examined the distribution of opioid prescribing across providers and patients and the extent to which concentrated distribution predicts opioid misuse. METHODS: Using 2013 Oregon Medicaid claims and the National Provider Identifier Registry, this study identified patients who filled at least one opioid prescription and providers who prescribed opioids for those patients (N=61,477 Medicaid beneficiaries). This study examined the distribution of opioid prescriptions by provider and patient, the extent to which high-volume opioid use was associated with potential opioid misuse, and how this association changed when patients received opioids from providers in the top decile of morphine-equivalent doses (MEQ) prescribed in 2013. This study used four indicators of opioid misuse: doctor and pharmacy shopping for opioid prescriptions, opioid prescription overlap, and opioid and benzodiazepine prescription overlap. RESULTS: Opioid use and prescriptions were heavily concentrated among the top 10% of opioid users and prescribers. Those high-volume opioid users and prescribers accounted for, respectively, 83.2% and 80.8% in MEQ of entire opioids prescribed. Patients' increasing use of opioids (by MEQ) was associated with most measures of opioid misuse. Patients receiving opioids from high-volume prescribers had a higher probability of opioid prescription overlap and opioid and benzodiazepine prescription overlap compared with other patients, but the difference was significant only among patients who received high doses of opioids, and the size of the difference was modest. CONCLUSIONS: Whereas current policies emphasize reducing opioid prescriptions

across all patients and providers, study results suggest that focusing policies on high-volume opioid users and prescribers may be more beneficial.

Kim, M. H., & von Gersdorff, H. (2016). Postsynaptic plasticity triggered by ca-permeable AMPA receptor activation in retinal amacrine cells. *Neuron,*

Amacrine cells are thought to be a major locus for mechanisms of light adaptation and contrast enhancement in the retina. However, the potential for plasticity in their AMPA receptor currents remains largely unknown. Using paired patch-clamp recordings between bipolar cell terminals and amacrine cells, we have simultaneously measured presynaptic membrane capacitance changes and EPSCs. Repetitive bipolar cell depolarizations, designed to maintain the same amount of exocytosis, nevertheless significantly potentiated evoked EPSCs in a subpopulation of amacrine cells. Likewise, repetitive iontophoresis (or puffs) of glutamate (or AMPA) onto the dendrites of amacrine cells also significantly potentiated evoked currents and [Ca2+]i rises. However, strong postsynaptic Ca2+ buffering with BAPTA abolished the potentiation and selective antagonists of Ca2+-permeable AMPA receptors also blocked the potentiation of AMPA-mediated currents. Together these results suggest that Ca2+ influx via Ca2+-permeable AMPA receptors can elicit a rapid form of postsynaptic plasticity in a subgroup of amacrine cell dendrites.

King, W. C., Chen, J. Y., Courcoulas, A. P., Mitchell, J. E., Wolfe, B. M., Patterson, E. J., et al. (2015). Objectively-measured sedentary time and cardiometabolic health in adults with severe obesity. *Preventive Medicine, 84*, 12-18.

It is unknown whether sedentary behavior is independently associated with the cardiometabolic health of adults with severe obesity. Additionally, there is debate regarding how best to derive meaningful indices of sedentary time (ST) from activity monitor data. A convenience sample of adults with severe obesity (N=927; 79% female, median age 45y, median body mass index (BMI) 46kg/m2) completed a research assessment at one of ten US hospitals in 2006-2009 prior to bariatric surgery. Cardiometabolic health was assessed via physical measures, fasting blood samples and medication use. Indices of ST were derived from StepWatch activity monitor data with minimum bout durations of 1min, 10min and 30min. Cross-sectional associations were examined. Median (25th, 75th percentile) ST was 9.3h/d (8.1, 10.5) in >/=1min bouts, 6.5h/d

(5.2, 8.0) in >/=10min bouts, or 3.2h/d (2.1, 4.5) in >/=30min bouts. Associations with ST were generally strongest with the >/=10min bout duration. Independent of moderate-to-vigorous intensity physical activity, BMI and other potential confounders, 1h/day ST in >/=10min bouts was associated with higher odds of diabetes by 15% (95%CI: 1.05-1.26), metabolic syndrome by 12% (95%CI: 1.01-1.24) and elevated blood pressure by 14% (95%CI: 1.02-1.26), and was associated with 1.4cm (95%CI: 0.9-1.9) larger waist circumference. Findings indicate the importance of considering ST as a distinct health risk among adults with severe obesity, and suggest a 10min minimum duration may be preferable to 1min or 30min for establishing ST from activity monitor data.

King, W. C., Chen, J. -., Courcoulas, A. P., Mitchell, J. E., Wolfe, B. M., Patterson, E. J., et al. (2016). Objectively-measured sedentary time and cardiometabolic health in adults with severe obesity. *Preventive Medicine, 84*, 12-18.

It is unknown whether sedentary behavior is independently associated with the cardiometabolic health of adults with severe obesity. Additionally, there is debate regarding how best to derive meaningful indices of sedentary time (ST) from activity monitor data. A convenience sample of adults with severe obesity (N=927; 79% female, median age 45 y, median body mass index (BMI) 46 kg/m2) completed a research assessment at one of ten US hospitals in 2006-2009 prior to bariatric surgery. Cardiometabolic health was assessed via physical measures, fasting blood samples and medication use. Indices of ST were derived from StepWatch™ activity monitor data with minimum bout durations of 1 min, 10 min and 30 min. Cross-sectional associations were examined. Median (25th, 75th percentile) ST was 9.3 h/d (8.1, 10.5) in ≥1 min bouts, 6.5 h/d (5.2, 8.0) in ≥10min bouts, or 3.2 h/d (2.1, 4.5) in ≥30 min bouts. Associations with ST were generally strongest with the ≥10 min bout duration. Independent of moderate-to-vigorous intensity physical activity, BMI and other potential confounders, 1h/day ST in ≥10min bouts was associated with higher odds of diabetes by 15% (95%CI: 1.05-1.26), metabolic syndrome by 12% (95%CI: 1.01-1.24) and elevated blood pressure by 14% (95%CI: 1.02-1.26), and was associated with 1.4 cm (95%CI: 0.9-1.9) larger waist circumference. Findings indicate the importance of considering ST as a distinct health risk among adults with severe obesity, and

suggest a 10 min minimum duration may be preferable to 1 min or 30 min for establishing ST from activity monitor data. © 2015 Elsevier Inc.

Klaassen, Z., Howard, L., Terris, M. K., Aronson, W. J., Cooperberg, M. R., Amling, C. L., et al. (2015). Does larger tumor volume explain the higher prostate specific antigen levels in black men with prostate cancer-results from the SEARCH database. *Cancer Epidemiology, 39*(6), 1066-1070. Objectives: To assess whether larger tumor volume in black men explains higher presurgical PSA levels versus white men with prostate cancer. Methods: We retrospectively analyzed 1904 men from the Shared Equal Access Regional Cancer Hospital database who underwent radical prostatectomy from 1990 to 2013. Geometric mean of tumor volume and preoperative PSA for each race were estimated from multivariable linear regression models. Results: There were 1104 (58%) white men and 800 (42%) black men. Black men were younger (60.2 vs. 62.9 years, p< 0.001) had a higher PSA (6.7 vs. 6.0 ng/mL, p< 0.001), more positive margins (47 vs. 38%, p< 0.001), and seminal vesicle invasion (13 vs. 9%, p=0.007). White patients had higher clinical stage (p< 0.001) and greater median tumor volume (6.0 vs. 5.3 gm, p=0.011). After multivariable adjustment (except for PSA), white men had smaller mean tumor volumes (5.2 vs. 5.8 gm, p=0.011). When further adjusted for PSA, there was no racial difference in mean tumor volume (p=0.34). After multivariable adjustment, black men had higher mean PSAs vs. white men (7.5 vs. 6.1 ng/mL, p< 0.001). Results were similar after further adjusting for tumor volume: black men had 16% higher mean PSAs versus white men (7.4 vs. 6.2 ng/mL, p< 0.001). Conclusions: In this study of men undergoing radical prostatectomy at multiple equal access medical centers, racial differences in tumor volume did not explain higher presurgical PSA levels in black versus white men. The exact reason for higher PSA values in black men remains unclear. © 2015 Elsevier Ltd.

Kleven, M. D., Enns, C. A., & Zhang, A. S. (2016). BMP6 mutations take their place in iron overload diseases. *Gastroenterology,*

Klionsky, D. J., Abdelmohsen, K., Abe, A., Abedin, M. J., Abeliovich, H., Acevedo Arozena, A., et al. (2016). Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy, 12*(1), 1-222.

Klyuchnikov, E., Bacher, U., Woo Ahn, K., Carreras, J., Kröger, N. M., Hari, P. N., et al. (2016). Long-term survival outcomes of reduced-intensity allogeneic or autologous transplantation in relapsed grade 3 follicular lymphoma. *Bone Marrow Transplantation, 51*(1), 58-66.
Grade 3 follicular lymphoma (FL) has aggressive clinical behavior. To evaluate the optimal first transplantation approach in relapsed/refractory grade 3 FL patients, we compared the long-term outcomes after allogeneic (allo-) vs autologous hematopoietic cell transplantation (auto-HCT) in the rituximab era. A total of 197 patients undergoing first reduced-intensity conditioning (RIC) allo-HCT or first auto-HCT during 2000-2012 were included. Rituximab-naive patients were excluded. Allo-HCT recipients were younger, more heavily pretreated and had a longer interval between diagnosis and HCT. The 5-year probabilities of non-relapse mortality (NRM), relapse/progression, PFS and overall survival (OS) for auto-HCT vs allo-HCT groups were 4% vs 27% (P<0.001), 61% vs 20% (P<0.001), 36% vs 51% (P=0.07) and 59% vs 54% (P=0.7), respectively. On multivariate analysis, auto-HCT was associated with reduced risk of NRM (relative risk (RR)=0.20; P=0.001). Within the first 11 months post HCT, auto- and allo-HCT had similar risks of relapse/progression and PFS. Beyond 11 months, auto-HCT was associated with higher risk of relapse/progression (RR=21.3; P=0.003) and inferior PFS (RR=3.2; P=0.005). In the first 24 months post HCT, auto-HCT was associated with improved OS (RR=0.42; P=0.005), but in long-time survivors (beyond 24 months) it was associated with inferior OS (RR=3.6; P=0.04). RIC allo-HCT as the first transplant approach can provide improved PFS and OS, in long-term survivors. © 2016 Macmillan Publishers Limited. All rights reserved.

Kozhimannil, K. B., Thao, V., Hung, P., Tilden, E., Caughey, A. B., & Snowden, J. M. (2015). Association between hospital birth volume and maternal morbidity among low-risk pregnancies in rural, urban, and teaching hospitals in the united states. *American Journal of Perinatology,*
Objectives This study aims to examine the relationship between hospital birth volume and multiple maternal morbidities among low-risk pregnancies in rural hospitals, urban non-teaching hospitals, and urban teaching hospitals, using a representative sample of U.S. hospitals. Study Design Using the 2011 Nationwide Inpatient Sample from 607 hospitals, we identified 508,146 obstetric deliveries meeting low-risk criteria and compared outcomes across hospital volume categories. Outcomes include postpartum hemorrhage (PPH), chorioamnionitis, endometritis,

blood transfusion, severe perineal laceration, and wound infection. Results Hospital birth volume was more consistently related to PPH than to other maternal outcomes. Lowest-volume rural (< 200 births) and non-teaching (< 650 births) hospitals had 80% higher odds (adjusted odds ratio [AOR] = 1.80; 95% CI = 1.56–2.08) and 39% higher odds (AOR = 1.39; 95% CI = 1.26–1.53) of PPH respectively, than those in corresponding high-volume hospitals. However, in urban teaching hospitals, delivering in a lower-volume hospital was associated with 14% lower odds of PPH (AOR = 0.86; 95% CI = 0.80–0.93). Deliveries in rural hospitals had 31% higher odds of PPH than urban teaching hospitals (AOR = 1.31; 95% CI = 1.13–1.53). Conclusions Low birth volume was a risk factor for PPH in both rural and urban non-teaching hospitals, but not in urban teaching hospitals, where higher volume was associated with greater odds of PPH.

Kozhimannil, K. B., Thao, V., Hung, P., Tilden, E., Caughey, A. B., & Snowden, J. M. (2016). Association between hospital birth volume and maternal morbidity among low-risk pregnancies in rural, urban, and teaching hospitals in the united states. *American Journal of Perinatology,* Objectives This study aims to examine the relationship between hospital birth volume and multiple maternal morbidities among low-risk pregnancies in rural hospitals, urban non-teaching hospitals, and urban teaching hospitals, using a representative sample of U.S. hospitals. Study Design Using the 2011 Nationwide Inpatient Sample from 607 hospitals, we identified 508,146 obstetric deliveries meeting low-risk criteria and compared outcomes across hospital volume categories. Outcomes include postpartum hemorrhage (PPH), chorioamnionitis, endometritis, blood transfusion, severe perineal laceration, and wound infection. Results Hospital birth volume was more consistently related to PPH than to other maternal outcomes. Lowest-volume rural (< 200 births) and non-teaching (< 650 births) hospitals had 80% higher odds (adjusted odds ratio [AOR] = 1.80; 95% CI = 1.56-2.08) and 39% higher odds (AOR = 1.39; 95% CI = 1.26-1.53) of PPH respectively, than those in corresponding high-volume hospitals. However, in urban teaching hospitals, delivering in a lower-volume hospital was associated with 14% lower odds of PPH (AOR = 0.86; 95% CI = 0.80-0.93). Deliveries in rural hospitals had 31% higher odds of PPH than urban teaching hospitals (AOR = 1.31; 95% CI = 1.13-1.53). Conclusions Low birth volume was

a risk factor for PPH in both rural and urban non-teaching hospitals, but not in urban teaching hospitals, where higher volume was associated with greater odds of PPH.

Kranjec, I., & Pavčnik, D. (2015). The first percutaneous coronary intervention performed on the patient with acute myocardial infarction. A clinical case report. [Prva perkutana koronarna revaskularizacija pri bolniku z akutnim miokardnim infarktom. Prikaz kliničnega primera] *Zdravniski Vestnik, 84*(11), 780-783.

A case of a patient suffering from myocardial infarction with ST-segment elevation 26 years ago is presented. Systemic thrombolysis was not possible due to recent bleeding from a duodenal ulcer. Therefore, an urgent percutaneous coronary revascularization was successfully carried out, the first such procedure in Slovenia. The revascularization was successful, the hospital course uneventful, and the patient remained asymptomatic for the following two years. Despite the progression of coronary atherosclerosis, the infarction-affected artery remained patent.

Ku, C. A., Pennesi, M. E., & Hariprasad, S. M. (2016). Gene therapy trial update: A primer for vitreoretinal specialists. *Ophthalmic Surgery Lasers and Imaging Retina, 47*(1), 6-12.

Kurillo, G., Ofli, F., Marcoe, J., Gorman, P., Jimison, H., Pavel, M., et al. (2015). In Salvendy G., Zhou J. & Salvendy G.(Eds.), *Multi-disciplinary design and in-home evaluation of kinect-based exercise coaching system for elderly* Springer Verlag.

Physical activity is recognized as one of the most effective measures to reduce risk of injury and to improve the quality of life in elderly. Many of the elderly however lack the motivation, confidence and skills to engage in regular exercise activity. One of the promising approaches is semi-automated coaching that combines exercise monitoring and interaction with a health coach. To gain a better understanding of the needs and challenges faced by the elderly when using such systems, we developed Kinect-based interactive exercise system to encourage healthy behavior and increase motivation to exercise. We present the multi-disciplinary design process and evaluation of the developed system in a home environment where various real-world challenges had to be overcome.

Kurz, M. C., Prince, D. K., Christenson, J., Carlson, J., Stub, D., Cheskes, S., et al. (2016). Association of advanced airway device with chest compression fraction during out-of-hospital cardiopulmonary arrest. *Resuscitation, 98*, 35-40.

Background: Select Emergency Medical Services (EMS) practitioners substitute endotracheal intubation (ETI) with supraglottic airway (SGA) insertion to minimize CPR chest compression interruptions, but the resulting effects upon chest compression fraction (CCF) are unknown. We sought to determine the differences in CCF between adult out-of-hospital cardiac arrest (OHCA) receiving ETI and those receiving SGA. Methods: We studied adult, non-traumatic OHCA patients enrolled in the Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation using an Impedance valve and an Early vs. Delayed analysis (PRIMED) trial. Chest compressions were measured using compression or thoracic impedance sensors. We limited the analysis to those receiving ETI or SGA (Combitube, King Laryngeal Tube, or Laryngeal Mask Airway) and >2. min of chest compression data before and after airway insertion. We compared CCF between ETI and SGA before and after airway insertion, adjusting for age, sex, witnessed arrest, bystander CPR, shockable initial rhythm, public location, PRIMED trial arm, and regional ROC center. We also compared the change in CCF for each airway technique. Results: Of 14,955 patients enrolled in the ROC PRIMED trial, we analyzed 2767 cases, including 2051 ETI, 671 SGA, and 45 both. Among subjects in this investigation the mean age was 66.4 years with a male predominace, 46% with witnessed event, 37% receiving bystander CPR, and 22% presenting with an initially shockable rhythm. Pre- and post-airway CCF was higher for SGA than ETI (SGA pre-airway CCF 73.2% [95%CI: 71.6-74.7%] vs. ETI 70.6% [95%CI: 69.7-71.5%]; post-airway 76.7% [95%CI: 75.2-78.1%] vs. 72.4% [95%CI: 71.5-73.3%]). After adjusting for potential confounders, these significant changes persisted (pre-airway difference 2.2% favoring SGA, p-value. =. 0.046; post-airway 3.4% favoring SGA, p=. 0.001). Conclusion: In patients with OHCA, we detected a slightly higher rate of CCF in patients for whom a SGA was inserted, both before and after insertion. However, the actual differences were so small, that in the context of this observational, secondary analysis, it is unclear if this represents a clinically significant difference.

Kyrylkova, K., Iwaniec, U. T., Philbrick, K. A., & Leid, M. (2015). BCL11B regulates sutural patency in the mouse craniofacial skeleton. *Developmental Biology,*

The transcription factor BCL11B plays essential roles during development of the immune, nervous, and cutaneous systems. Here we show that BCL11B is expressed in both osteogenic and sutural mesenchyme of the developing craniofacial complex. Bcl11b -/- mice exhibit increased proliferation of osteoprogenitors, premature osteoblast differentiation, and enhanced skull mineralization leading to synostoses of facial and calvarial sutures. Ectopic expression of Fgfr2c, a gene implicated in craniosynostosis in mice and humans, and that of Runx2 was detected within the affected sutures of Bcl11b -/- mice. These data suggest that ectopic expression of Fgfr2c in the sutural mesenchyme, without concomitant changes in the expression of FGF ligands, appears to induce the RUNX2-dependent osteogenic program and craniosynostosis in Bcl11b -/- mice. © 2015 Elsevier Inc.

Laderas, T. G., Heiser, L. M., & Sönmez, K. (2015). A network-based model of oncogenic collaboration for prediction of drug sensitivity. *Frontiers in Genetics, 6*(DEC)

Tumorigenesis is a multi-step process, involving the acquisition of multiple oncogenic mutations that transform cells, resulting in systemic dysregulation that enables proliferation, invasion, and other cancer hallmarks. The goal of precision medicine is to identify therapeutically-actionable mutations from large-scale omic datasets. However, the multiplicity of oncogenes required for transformation, known as oncogenic collaboration, makes assigning effective treatments difficult. Motivated by this observation, we propose a new type of oncogenic collaboration where mutations in genes that interact with an oncogene may contribute to the oncogene's deleterious potential, a new genomic feature that we term "surrogate oncogenes." Surrogate oncogenes are representatives of these mutated subnetworks that interact with oncogenes. By mapping mutations to a protein-protein interaction network, we determine the significance of the observed distribution using permutation-based methods. For a panel of 38 breast cancer cell lines, we identified a significant number of surrogate oncogenes in known oncogenes such as BRCA1 and ESR1, lending credence to this approach. In addition, using Random Forest Classifiers, we show that these significant surrogate oncogenes predict drug sensitivity for 74 drugs in the breast cancer cell lines with a mean error rate of 30.9%. Additionally, we show that surrogate

oncogenes are predictive of survival in patients. The surrogate oncogene framework incorporates unique or rare mutations from a single sample, and therefore has the potential to integrate patient-unique mutations into drug sensitivity predictions, suggesting a new direction in precision medicine and drug development. Additionally, we show the prevalence of significant surrogate oncogenes in multiple cancers from The Cancer Genome Atlas, suggesting that surrogate oncogenes may be a useful genomic feature for guiding pancancer analyses and assigning therapies across many tissue types. © 2015 Laderas, Heiser and Sönmez.

Ladermann, A., Denard, P. J., Abrassart, S., & Schwitzguebel, A. J. (2016). Achilles tendon allograft for an irreparable massive rotator cuff tear with bony deficiency of the greater tuberosity. *Knee Surgery, Sports Traumatology, Arthroscopy : Official Journal of the ESSKA,*
Management of combined bony and tendinous deficiency of the posterosuperior rotator cuff represents a challenge in young patients. In this case report, a 44-year-old woman that presented an osteonecrosis of the greater tuberosity had a pseudoparalytic shoulder. She beneficiated from a fresh-frozen Achilles tendon allograft with calcaneal bone, which was used to reconstruct the rotator cuff and the concomitant bony defect. At 12-month follow-up, the patient was pain free and had complete range of motion, normal strength, a SANE score of 95 and radiographically the allograft was healed. An Achilles tendon allograft may therefore be a viable surgical option to reconstruct a combine posterosuperior rotator cuff tear and greater tuberosity bone defect. Level of evidence IV.

Lasater, K., Nielsen, A. E., Stock, M., & Ostrogorsky, T. L. (2015). Evaluating the clinical judgment of newly hired staff nurses. *Journal of Continuing Education in Nursing, 46*(12), 563-571.
Assessing newly hired nurses' readiness for practice is critical for safe practice and the quality care of patients; therefore, hospitals need effective assessment strategies to promote clinical judgment development. One large medical center hospital developed a process to assess new hires' clinical judgment, using case studies. This article describes the assessment process and reports fi ndings from a retrospective analysis of the clinical judgment competency of the participants. The fi ndings suggest that more orientation time and experience are needed for less-experienced nurses (<3 years) and experienced nurses who have not practiced in acute

care. The research concludes that practice and academic educators must work more closely for a smoother transition of novice nurses into practice. © SLACK Incorporated.

Lee, B., Diaz, G. A., Rhead, W., Lichter-Konecki, U., Feigenbaum, A., Berry, S. A., et al. (2016). Glutamine and hyperammonemic crises in patients with urea cycle disorders. *Molecular Genetics and Metabolism, 117*(1), 27-32.

Blood ammonia and glutamine levels are used as biomarkers of control in patients with urea cycle disorders (UCDs). This study was undertaken to evaluate glutamine variability and utility as a predictor of hyperammonemic crises (HACs) in UCD patients. Methods: The relationships between glutamine and ammonia levels and the incidence and timing of HACs were evaluated in over 100 adult and pediatric UCD patients who participated in clinical trials of glycerol phenylbutyrate. Results: The median (range) intra-subject 24-hour coefficient of variation for glutamine was 15% (8-29%) as compared with 56% (28%-154%) for ammonia, and the correlation coefficient between glutamine and concurrent ammonia levels varied from 0.17 to 0.29. Patients with baseline (fasting) glutamine values >. 900. μmol/L had higher baseline ammonia levels (mean [SD]: 39.6 [26.2]. μmol/L) than patients with baseline glutamine ≤. 900. μmol/L (26.6 [18.0]. μmol/L). Glutamine values >. 900. μmol/L during the study were associated with an approximately 2-fold higher HAC risk (odds ratio [OR] = 1.98; p = 0.173). However, glutamine lost predictive significance (OR = 1.47; p = 0.439) when concomitant ammonia was taken into account, whereas the predictive value of baseline ammonia ≥. 1.0 upper limit of normal (ULN) was highly statistically significant (OR = 4.96; p = 0.013). There was no significant effect of glutamine >. 900. μmol/L on time to first HAC crisis (hazard ratio [HR] = 1.14; p = 0.813), but there was a significant effect of baseline ammonia ≥. 1.0 ULN (HR = 4.62; p = 0.0011). Conclusions: The findings in this UCD population suggest that glutamine is a weaker predictor of HACs than ammonia and that the utility of the predictive value of glutamine will need to take into account concurrent ammonia levels. © 2015 The Authors.

Lee, V. R., Darney, B. G., Snowden, J. M., Main, E. K., Gilbert, W., Chung, J., et al. (2016). Term elective induction of labour and perinatal outcomes in obese women: Retrospective cohort study. *BJOG: An International Journal of Obstetrics and Gynaecology, 123*(2), 271-278.

Objective To compare perinatal outcomes between elective induction of labour (eIOL) and expectant management in obese women. Design Retrospective cohort study. Setting Deliveries in California in 2007. Population Term, singleton, vertex, nonanomalous deliveries among obese women (n = 74 725). Methods Women who underwent eIOL at 37 weeks were compared with women who were expectantly managed at that gestational age. Similar comparisons were made at 38, 39, and 40 weeks. Results were stratified by parity. Chi-square tests and multivariable logistic regression were used for statistical comparison. Main outcome measures Method of delivery, severe perineal lacerations, postpartum haemorrhage, chorioamnionitis, macrosomia, shoulder dystocia, brachial plexus injury, respiratory distress syndrome. Results The odds of caesarean delivery were lower among nulliparous women with eIOL at 37 weeks [odds ratio (OR) 0.55, 95% confidence interval (CI) 0.34-0.90] and 39 weeks (OR 0.77, 95% CI 0.63-0.95) compared to expectant management. Among multiparous women with a prior vaginal delivery, eIOL at 37 (OR 0.39, 95% CI 0.24-0.64), 38 (OR 0.65, 95% CI 0.51-0.82), and 39 weeks (OR 0.67, 95% CI 0.56-0.81) was associated with lower odds of caesarean. Additionally, eIOL at 38, 39, and 40 weeks was associated with lower odds of macrosomia. There were no differences in the odds of operative vaginal delivery, lacerations, brachial plexus injury or respiratory distress syndrome. Conclusions In obese women, term eIOL may decrease the risk of caesarean delivery, particularly in multiparas, without increasing the risks of other adverse outcomes when compared with expectant management. Tweetable abstract Elective induction of labour in obese women does not increase risk of caesarean or other perinatal morbidities. © 2015 Royal College of Obstetricians and Gynaecologists.

Leo, M. C., McMullen, C., Wilfond, B. S., Lynch, F. L., Reiss, J. A., Gilmore, M. J., et al. (2016). Patients' ratings of genetic conditions validate a taxonomy to simplify decisions about preconception carrier screening via genome sequencing. *American Journal of Medical Genetics.Part A,*

Advances in genome sequencing and gene discovery have created opportunities to efficiently assess more genetic conditions than ever before. Given the large number of conditions that can be screened, the implementation of expanded carrier screening using genome sequencing will require practical methods of simplifying decisions about the conditions for which patients want to

be screened. One method to simplify decision making is to generate a taxonomy based on expert judgment. However, expert perceptions of condition attributes used to classify these conditions may differ from those used by patients. To understand whether expert and patient perceptions differ, we asked women who had received preconception genetic carrier screening in the last 3 years to fill out a survey to rate the attributes (predictability, controllability, visibility, and severity) of several autosomal recessive or X-linked genetic conditions. These conditions were classified into one of five taxonomy categories developed by subject experts (significantly shortened lifespan, serious medical problems, mild medical problems, unpredictable medical outcomes, and adult-onset conditions). A total of 193 women provided 739 usable ratings across 20 conditions. The mean ratings and correlations demonstrated that participants made distinctions across both attributes and categories. Aggregated mean attribute ratings across categories demonstrated logical consistency between the key features of each attribute and category, although participants perceived little difference between the mild and serious categories. This study provides empirical evidence for the validity of our proposed taxonomy, which will simplify patient decisions for results they would like to receive from preconception carrier screening via genome sequencing. (c) 2016 Wiley Periodicals, Inc.

Liko, J., Guzman-Cottrill, J. A., & Cieslak, P. R. (2016). Notes from the field: Subacute sclerosing panencephalitis death - oregon, 2015. *MMWR.Morbidity and Mortality Weekly Report, 65*(1), 10-11.

In 2015, the Oregon Health Authority was notified of the death of a boy with subacute sclerosing panencephalitis (SSPE), a rare and fatal complication of measles. The patient, aged 14 years, had reportedly been vaccinated against measles in the Philippines at age 8 months. However, the patient contracted measles at age 1 year while still in the Philippines. He had been well until 2012, when his neurodegenerative symptoms began. After the diagnosis of SSPE was made, the patient remained in home hospice care until his death. Investigators from the Oregon Health Authority and the Oregon Health and Science University reviewed the patient's medical records and interviewed the parents. Vaccination against measles can prevent not only acute measles and its complications, but also SSPE.

Lin, H., Song, P., Zhao, Y., Xue, L. J., Liu, Y., & Chu, C. Q. (2015). Targeting Th17 cells with small molecules and small interference RNA. *Mediators of Inflammation, 2015*, 290657.

T helper 17 (Th17) cells play a central role in inflammatory and autoimmune diseases via the production of proinflammatory cytokines interleukin- (IL-) 17, IL-17F, and IL-22. Anti-IL-17 monoclonal antibodies show potent efficacy in psoriasis but poor effect in rheumatoid arthritis (RA) and Crohn's disease. Alternative agents targeting Th17 cells may be a better way to inhibit the development and function of Th17 cells than antibodies of blocking a single effector cytokine. Retinoic acid-related orphan receptor gamma t (RORgammat) which acts as the master transcription factor of Th17 differentiation has been an attractive pharmacologic target for the treatment of Th17-mediated autoimmune disease. Recent progress in technology of chemical screen and engineering nucleic acid enable two new classes of therapeutics targeting RORgammat. Chemical screen technology identified several small molecule specific inhibitors of RORgammat from a small molecule library. Systematic evolution of ligands by exponential enrichment (SELEX) technology enabled target specific aptamers to be isolated from a random sequence oligonucleotide library. In this review, we highlight the development and therapeutic potential of small molecules inhibiting Th17 cells by targeting RORgammat and aptamer mediated CD4(+) T cell specific delivery of small interference RNA against RORgammat gene expression to inhibit pathogenic effector functions of Th17 lineage.

Linch, S. N., Kasiewicz, M. J., McNamara, M. J., Hilgart-Martiszus, I. F., Farhad, M., & Redmond, W. L. (2016). Combination OX40 agonism/CTLA-4 blockade with HER2 vaccination reverses T-cell anergy and promotes survival in tumor-bearing mice. *Proceedings of the National Academy of Sciences of the United States of America, 113*(3), E319-27.

Immunotherapy is gathering momentum as a primary therapy for cancer patients. However, monotherapies have limited efficacy in improving outcomes and benefit only a subset of patients. Combination therapies targeting multiple pathways can augment an immune response to improve survival further. Here, we demonstrate that dual aOX40 (anti-CD134)/aCTLA-4 (anti-cytotoxic T-lymphocyte-associated protein 4) immunotherapy generated a potent antigen-specific CD8 T-cell response, enhancing expansion, effector function, and memory T-cell persistence. Importantly, OX40 and CTLA-4 expression on CD8 T cells was critical for promoting their maximal expansion

following combination therapy. Animals treated with combination therapy and vaccination using anti-DEC-205 (dendritic and epithelial cells, 205 kDa)-HER2 (human epidermal growth factor receptor 2) had significantly improved survival in a mammary carcinoma model. Vaccination with combination therapy uniquely restricted Th2-cytokine production by CD4 cells, relative to combination therapy alone, and enhanced IFNgamma production by CD8 and CD4 cells. We observed an increase in MIP-1alpha (macrophage inflammatory protein-1alpha)/CCL3 [chemokine (C-C motif) ligand 3], MIP-1beta/CCL4, RANTES (regulated on activation, normal T-cell expressed and excreted)/CCL5, and GM-CSF production by CD8 and CD4 T cells following treatment. Furthermore, this therapy was associated with extensive tumor destruction and T-cell infiltration into the tumor. Notably, in a spontaneous model of prostate adenocarcinoma, vaccination with combination therapy reversed anergy and enhanced the expansion and function of CD8 T cells recognizing a tumor-associated antigen. Collectively, these data demonstrate that the addition of a vaccine with combined aOX40/aCTLA-4 immunotherapy augmented antitumor CD8 T-cell function while limiting Th2 polarization in CD4 cells and improved overall survival.

Little, S. E., Orav, E. J., Robinson, J. N., Caughey, A. B., & Jha, A. K. (2015). The relationship between variations in cesarean delivery and regional healthcare utilization in the U.S. *American Journal of Obstetrics and Gynecology,*

BACKGROUND: Cesarean delivery rates vary widely across the U.S. Healthcare utilization in many other areas of medicine also varies widely across the U.S.; it is unknown whether the variation in cesarean delivery rates across U.S. communities is correlated with this broader underlying variation in healthcare utilization patterns. OBJECTIVE(S): To determine if the variation in cesarean delivery rates across U.S. communities is correlated with other measures of healthcare utilization in that community. STUDY DESIGN: We performed a population-based observational study that combined multiple national data sources, including 2010 birth certificate data and Medicare claims data. Cesarean delivery rates in each U.S. community, as defined by the Hospital Service Area (HSA), were calculated as was Medicare total spending per beneficiary and hospital days in the last 6 months. Cesarean delivery and Medicare spending were on different patient populations; the Medicare variables were used to characterize the broader healthcare utilization and spending pattern of that community. We examined the relationship between a community's

cesarean delivery rates and these measures of healthcare utilization using Pearson correlation coefficients. We also stratified by quartile of Medicare spending and hospital use in the last 6 months of life and calculated the cesarean delivery rates per quartile, adjusting for underlying differences in patient characteristics, demographics, hospital structure and the malpractice environment using a least-squared means method. We compared the amount of variation in cesarean delivery rates across communities that could be explained by differences in healthcare utilization patterns to the amount of variation explained by other factors using the R-squared from multivariate models. RESULTS: Cesarean delivery rates varied from 4% to 65% across communities in the U.S. Cesarean delivery rates were positively correlated with total Medicare spending ($r=0.48$; $p<0.001$) and hospital use in the last 6 months of life ($r=0.45$; $p<0.001$). Similar variation was seen in nulliparous women with a term fetus in vertex presentation (NTSV cesareans), a common subset used for analyzing cesarean delivery rates. Communities in the lowest quartile of Medicare spending had the lowest rates of cesarean delivery (29.1% versus 35.7% in the highest quartile, $p<0.001$ for differences across quartiles), a difference that persisted after adjustment (29.5 versus 31.8%; $p<0.001$). Similar results were seen for NTSV cesareans and when stratifying by hospital days in the last 6 months of life. Overall, 28.6% of the total variation in cesarean rates was explained by differences in healthcare utilization patterns, as compared to 16.6% by differences in obstetric procedures, 7.9% by hospital structure and 2.3% by variations in the malpractice environment. Of the 56.3% of variation that was unexplained by differences in patient characteristics and area demographics, 8.2% could be accounted for by differences in healthcare utilization patterns, as compared to 4.6% by differences in obstetric procedures, 2.1% by hospital structure and 1.2% by variation in the malpractice environment. CONCLUSION(S): Cesarean delivery rates vary widely across U.S. communities; this variation is broadly correlated with the variation seen in other measures of healthcare utilization across U.S. communities.

Liu, J., You, L., Zheng, J., Ross, A. M., & Liu, K. (2016). Effects of work environment on quality of care in ICUs: A multisite survey in china. *Journal of Nursing Care Quality,*

This study estimated the effects of the work environment on the quality of care in intensive care units (ICUs). Nurses in ICUs with good work environments or high nurse staffing were

significantly less likely to report poor or fair quality of care (odds ratio [OR] = 0.37-0.47), rationing of nursing care (OR = 0.38-0.76), and health care-associated infections (OR = 0.28-0.68). Favorable ICU work environments and adequate nurse staffing can predict better quality of care.

Loftis, J. M. (2015). Commentary: Methamphetamine mediates immune dysregulation in a murine model of chronic viral infection. *Frontiers in Microbiology, 6*(DEC)

Lominac, K. D., Quadir, S. G., Barrett, H. M., McKenna, C. L., Schwartz, L. M., Ruiz, P. N., et al. (2016). Prefrontal glutamate correlates of methamphetamine sensitization and preference. *The European Journal of Neuroscience,*

Methamphetamine (MA) is a widely abused, highly addictive, psychostimulant that elicits pronounced deficits in neurocognitive function related to hypo-functioning of the prefrontal cortex (PFC). Our understanding of how repeated methamphetamine impacts excitatory glutamatergic transmission within the PFC is limited, as is information about the relation between PFC glutamate and addiction vulnerability/resiliency. In vivo microdialysis and immunoblotting studies characterized the effects of methamphetamine (10 injections of 2 mg/kg, IP) upon extracellular glutamate in C57BL/6J mice and upon glutamate receptor and transporter expression, within the medial PFC. Glutamatergic correlates of both genetic and idiopathic variance in MA preference/intake were determined through studies of high versus low MA-drinking selectively bred mouse lines (MAHDR versus MALDR, respectively) and inbred C57BL/6J mice exhibiting spontaneously divergent place-conditioning phenotypes. Repeated methamphetamine sensitized drug-induced glutamate release and lowered indices of NMDA receptor expression in C57BL/6J mice, but did not alter basal extracellular glutamate content or total protein expression of Homer proteins, or metabotropic or AMPA glutamate receptors. Elevated basal glutamate, blunted methamphetamine-induced glutamate release and ERK activation, as well as reduced protein expression of mGlu2/3 and Homer2a/b were all correlated biochemical traits of selection for high versus low methamphetamine drinking, and Homer2a/b levels were inversely correlated with the motivational valence of methamphetamine in C57BL/6J mice. These data provide novel evidence that repeated, low-dose, methamphetamine is sufficient to perturb pre- and post-synaptic

aspects of glutamate transmission within the medial PFC and that glutamate anomalies within this region may contribute to both genetic and idiopathic variance in methamphetamine addiction vulnerability/resiliency. This article is protected by copyright. All rights reserved.

Lomniczi, A., & Ojeda, S. R. (2016). *The emerging role of epigenetics in the regulation of female puberty* S. Karger AG.

In recent years the pace of discovering the molecular and genetic underpinnings of the pubertal process has accelerated considerably. Genes required for human puberty to occur have been identified and evidence has been provided suggesting that the initiation of puberty requires coordinated changes in the output of a multiplicity of genes organized into functional networks. Recent evidence suggests that a dual mechanism of epigenetic regulation affecting the transcriptional activity of neurons involved in stimulating gonadotropin-releasing hormone release plays a fundamental role in the timing of puberty. The Polycomb group (PcG) of transcriptional silencers appears to be a major component of the repressive arm of this mechanism. PcG proteins prevent the premature initiation of female puberty by silencing the Kiss1 gene in kisspeptin neurons of the arcuate nucleus (ARC) of the hypothalamus. Because the abundance of histone marks either catalyzed by - or associated with - the Trithorax group (TrxG) of transcriptional activators increases at the time when PcG control subsides, it appears that the TrxG complex is the counteracting partner of PcG-mediated gene silencing. In this chapter, we discuss the concept that a switch from epigenetic repression to activation within ARC kisspeptin neurons is a core mechanism underlying the initiation of female puberty. © 2016 S. Karger AG, Basel.

Lonial, S., Weiss, B. M., Usmani, S. Z., Singhal, S., Chari, A., Bahlis, N. J., et al. (2015). Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): An open-label, randomised, phase 2 trial. *The Lancet,*

Background: New treatment options are needed for patients with multiple myeloma that is refractory to proteasome inhibitors and immunomodulatory drugs. We assessed daratumumab, a novel CD38-targeted monoclonal antibody, in patients with refractory multiple myeloma. Methods: In this open-label, multicentre, phase 2 trial done in Canada, Spain, and the USA,

patients (age ≥18 years) with multiple myeloma who were previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or were refractory to both proteasome inhibitors and immunomodulatory drugs, were randomly allocated in a 1:1 ratio to receive intravenous daratumumab 8 mg/kg or 16 mg/kg in part 1 stage 1 of the study, to decide the dose for further assessment in part 2. Patients received 8 mg/kg every 4 weeks, or 16 mg/kg per week for 8 weeks (cycles 1 and 2), then every 2 weeks for 16 weeks (cycles 3-6), and then every 4 weeks thereafter (cycle 7 and higher). The allocation schedule was computer-generated and randomisation, with permuted blocks, was done centrally with an interactive web response system. In part 1 stage 2 and part 2, patients received 16 mg/kg dosed as in part 1 stage 1. The primary endpoint was overall response rate (partial response [PR] + very good PR + complete response [CR] + stringent CR). All patients who received at least one dose of daratumumab were included in the analysis. The trial is registered with ClinicalTrials.gov, number NCT01985126. Findings: The study is ongoing. In part 1 stage 1 of the study, 18 patients were randomly allocated to the 8 mg/kg group and 16 to the 16 mg/kg group. Findings are reported for the 106 patients who received daratumumab 16 mg/kg in parts 1 and 2. Patients received a median of five previous lines of therapy (range 2-14). 85 (80%) patients had previously received autologous stem cell transplantation, 101 (95%) were refractory to the most recent proteasome inhibitors and immunomodulatory drugs used, and 103 (97%) were refractory to the last line of therapy. Overall responses were noted in 31 patients (29·2%, 95% CI 20·8-38·9)-three (2·8%, 0·6-8·0) had a stringent CR, ten (9·4%, 4·6-16·7) had a very good PR, and 18 (17·0%, 10·4-25·5) had a PR. The median time to first response was 1·0 month (range 0·9-5·6). Median duration of response was 7·4 months (95% CI 5·5-not estimable) and progression-free survival was 3·7 months (95% CI 2·8-4·6). The 12-month overall survival was 64·8% (95% CI 51·2-75·5) and, at a subsequent cutoff, median overall survival was 17·5 months (95% CI 13·7-not estimable). Daratumumab was well tolerated; fatigue (42 [40%] patients) and anaemia (35 [33%]) of any grade were the most common adverse events. No drug-related adverse events led to treatment discontinuation. Interpretation: Daratumumab monotherapy showed encouraging efficacy in heavily pretreated and refractory patients with multiple myeloma, with a favourable safety profile in this population of patients. Funding: Janssen Research & Development.

Love, J. N., Yarris, L. M., Santen, S. A., Kuhn, G. J., Gruppen, L. D., Coates, W. C., et al. (2016). A novel specialty-specific, collaborative faculty development opportunity in education research: Program evaluation at five years. *Academic Medicine : Journal of the Association of American Medical Colleges,*

PURPOSE: For the busy clinician-educator, accessing opportunities that develop the skills and knowledge necessary to perform education research can be problematic. The Medical Education Research Certification at Council of Emergency Medicine Residency Directors (MERC at CORD) Scholars' Program is a potential alternative. The current study evaluates the program's outcomes after five years. METHOD: The authors employed a quasi-experimental design in this study. The study population consisted of the initial five MERC at CORD cohorts (2009-2013). Development of a logic model informed Kirkpatrick-level outcomes. Data from annual pre/post surveys, an alumni survey (2014), and tracking of national presentations/peer-reviewed publications resulting from program projects served as outcome measurements. RESULTS: Over the first five years, 149 physicians participated in the program; 97 have completed six MERC workshops, and 63 have authored a national presentation and 30 a peer-reviewed publication based on program projects. Of the 79 participants responding to the pre- and postsurveys from the 2011-2013 cohorts, 65 (82%) reported significant improvement in skills and knowledge related to education research and would recommend the program. Of the 61 graduates completing the alumni survey, 58 (95%) indicated their new knowledge was instrumental beyond educational research, including promotion to new leadership positions, and 28 (47% of the 60 responding) reported initiating a subsequent multi-institutional education study. Of these, 57% (16/28) collaborated with one or more peers/mentors from their original program project. CONCLUSIONS: Kirkpatrick-level outcomes 1, 2, 3, and perhaps 4 demonstrate that the MERC at CORD program is successful in its intended purpose.

Loyo, M., & Wang, T. D. (2015). Revision rhinoplasty. *Clinics in Plastic Surgery,*

Revision rhinoplasty is one of the most challenging operations the facial plastic surgeon performs given the complex 3-dimensional anatomy of the nose and the psychological impact it has on patients. The intricate interplay of cartilages, bone, and soft tissue in the nose gives it its aesthetic and function. Facial harmony and attractiveness depends greatly on the nose given its

central position in the face. In the following article, the authors review common motivations and anatomic findings for patients seeking revision rhinoplasty based on the senior author's 30-year experience with rhinoplasty and a review of the literature. © 2015 Elsevier Inc.

Luh, J. Y., Harmon, M. W., Eng, T. Y., & Thomas, C. R. (2016). Radiation therapy in gastric and ocular marginal zone lymphomas. *Mayo Clinic Proceedings, 91*(1), 123.

Luna, D., Quispe, M., Gonzalez, Z., Alemrares, A., Risk, M., Garcia Aurelio, M., et al. (2015). In Georgiou A., Sarkar I.N. & de Azevedo Marques P.M.(Eds.), *User-centered design to develop clinical applications. literature review* IOS Press.

User-centered design is mentioned by Norman as 'the need for a design that uses the natural properties of the individuals, exploiting the relationships and constraints and focusing on the needs and interests of the user, in order to make the final products usable and understandable'. This is also important in health developments. The objective of this paper is to search and analyze articles in the healthcare field where user-centered design principles have been applied. We describe findings in this topic from articles published between January 1995 and September 2014. © 2015 IMIA and IOS Press.

Lund, A. W., Medler, T. R., Leachman, S. A., & Coussens, L. M. (2016). Lymphatic vessels, inflammation, and immunity in skin cancer. *Cancer Discovery, 6*(1), 22-35.

Skin is a highly ordered immune organ that coordinates rapid responses to external insult while maintaining self-tolerance. In healthy tissue, lymphatic vessels drain fluid and coordinate local immune responses; however, environmental factors induce lymphatic vessel dysfunction, leading to lymph stasis and perturbed regional immunity. These same environmental factors drive the formation of local malignancies, which are also influenced by local inflammation. Herein, we discuss clinical and experimental evidence supporting the tenet that lymphatic vessels participate in regulation of cutaneous inflammation and immunity, and are important contributors to malignancy and potential biomarkers and targets for immunotherapy. Significance: The tumor microenvironment and tumor-associated inflammation are now appreciated not only for their role in cancer progression but also for their response to therapy. The lymphatic vasculature is a less-appreciated component of this microenvironment that coordinates local inflammation and

immunity and thereby critically shapes local responses. A mechanistic understanding of the complexities of lymphatic vessel function in the unique context of skin provides a model to understand how regional immune dysfunction drives cutaneous malignancies, and as such lymphatic vessels represent a biomarker of cutaneous immunity that may provide insight into cancer prognosis and effective therapy. © 2016 American Association for Cancer Research.

Ma, J., Strub, P., Lv, N., Xiao, L., Camargo, C. A., Jr., Buist, A. S., et al. (2016). Pilot randomised trial of a healthy eating behavioural intervention in uncontrolled asthma. *European Respiratory Journal, 47*(1), 122-132.

Rigorous research on the benefit of healthy eating patterns for asthma control is lacking. We randomised 90 adults with objectively confirmed uncontrolled asthma and a low-quality diet (Dietary Approaches to Stop Hypertension (DASH) scores <6 out of 9) to a 6-month DASH behavioural intervention (n=46) or usual-care control (n=44). Intention-to-treat analyses used repeated-measures mixed models. Participants were middle-aged, 67% female and multiethnic. Compared with controls, intervention participants improved on DASH scores (mean change (95% CI) 0.6 (0, 1.1) versus 0.3 (0.8, 0.2); difference 0.8 (0.2, 1.5)) and the primary outcome, Asthma Control Questionnaire scores (0.2 (0.5, 0) versus 0 (0.3, 0.3); difference 0.2 (0.5, 0.1)) at 6 months. The mean group differences in changes in Mini Asthma Quality of Life Questionnaire overall and subdomain scores consistently favoured the intervention over the control group: overall 0.4 (95% CI 0, 0.8), symptoms 0.5 (0, 0.9), environment 0.4 (0.1, 1.0), emotions 0.4 (0.2, 0.9) and activities 0.3 (0, 0.7). These differences were modest, but potentially clinical significant. The DASH behavioural intervention improved diet quality with promising clinical benefits for better asthma control and functional status among adults with uncontrolled asthma. A full-scale efficacy trial is warranted. © ERS 2016.

MacDonald, K. D., Vesco, K. K., Funk, K. L., Donovan, J., Nguyen, T., Chen, Z., et al. (2016). Maternal body mass index before pregnancy is associated with increased bronchodilator dispensing in early childhood: A cross-sectional study. *Pediatric Pulmonology,*

RATIONALE: Maternal prepregnancy obesity has been associated with early wheeze and childhood asthma in their offspring. Some of these studies have been in minority, urban, and

disadvantaged populations using parental recall and questionnaires. The association of maternal prepregnancy obesity with bronchodilator dispensing to their offspring, in a primarily insured, non-urban, White population in the United States is unknown. OBJECTIVES AND METHODS: We conducted a retrospective cohort study using pharmacy dispensing data from the electronic medical records of a large United States health maintenance organization to examine the relationship between maternal prepregnancy body mass index (BMI) and inhaled bronchodilator dispensing in the offspring to 4 years of age. We included infants >/=37 weeks' gestation with birth weight >/=2.5 kg which yielded 6,194 mother-baby pairs. Maternal prepregnancy BMI was categorized as underweight (/=30 kg/m2). RESULTS: In the entire cohort, 27.6% of the offspring received a bronchodilator dispensing. This ranged from 19.2% in the offspring of underweight mothers to 31.3% of those born to obese mothers. In the fully adjusted model using normal BMI as the referent, children of obese mothers had a 22% higher rate of bronchodilator dispensing (adjusted OR = 1.22; 95%CI 1.05-1.41; P = 0.008). CONCLUSIONS: In this insured, non-urban, White population, maternal prepregnancy obesity was associated with bronchodilator dispensing in the offspring in early life. These results extend previous data and reaffirm the potential widespread public health impact that prepregnancy obesity may have on subsequent childhood respiratory health. Pediatr Pulmonol. (c) 2016 Wiley Periodicals, Inc.

Mancini, M., Chiari, L., Holmstrom, L., Salarian, A., & Horak, F. B. (2016). Validity and reliability of an IMU-based method to detect APAs prior to gait initiation. *Gait and Posture, 43*, 125-131. Anticipatory postural adjustments (APAs) prior to gait initiation have been largely studied in traditional, laboratory settings using force plates under the feet to characterize the displacement of the center of pressure. However clinical trials and clinical practice would benefit from a portable, inexpensive method for characterizing APAs. Therefore, the main objectives of this study were (1) to develop a novel, automatic IMU-based method to detect and characterize APAs during gait initiation and (2) to measure its test-retest reliability. Experiment I was carried out in the laboratory to determine the validity of the IMU-based method in 10 subjects with PD (OFF medication) and 12 control subjects. Experiment II was carried out in the clinic, to determine test-retest reliability of the IMU-based method in a different set of 17 early-to-moderate, treated subjects with PD (tested ON medication) and 17 age-matched control subjects. Results showed

that gait initiation characteristics (both APAs and 1st step) detected with our novel method were significantly correlated to the characteristics calculated with a force plate and motion analysis system. The size of APAs measured with either inertial sensors or force plate was significantly smaller in subjects with PD than in control subjects (p<. 0.05). Test-retest reliability for the gait initiation characteristics measured with inertial sensors was moderate-to-excellent (0.56. <. ICC. <. 0.82) for both groups.Our findings support the feasibility of automatically characterizing postural preparation and gait initiation with body-worn inertial sensors that would be practical for unsupervised clinical and home settings. © 2015 Elsevier B.V.

Mangla, A., & Gupta, S. (2015). Vascular complications post-transcatheter aortic valve procedures. *Indian Heart Journal,*

Transcatheter aortic valve replacement (TAVR) has rapidly emerged as the standard of care for severe symptomatic aortic stenosis in patients whose comorbidities put them at prohibitive risk for surgical aortic valve replacement (SAVR). Several trials have demonstrated superior outcomes with TAVR compared to medical management alone. TAVR has also shown favorable outcomes in patients at high risk for SAVR. TAVR can be associated with significant vascular complications, which adversely impact outcomes, and operators should be cognizant of their early recognition and appropriate management. In this article, we review the major vascular complications associated with TAVR, along with optimal prevention and management strategies. © 2015 Cardiological Society of India.

Mansoor, A. M., & Mansoor, S. E. (2016). IMAGES IN CLINICAL MEDICINE. lancisi's sign. *The New England Journal of Medicine, 374*(2), e2.

Mansoor, A. M., & Mansoor, S. E. (2016). Lancisi's sign. *New England Journal of Medicine, 374*(2), e2.

Marijon, E., Uy-Evanado, A., Dumas, F., Karam, N., Reinier, K., Teodorescu, C., et al. (2016). Warning symptoms are associated with survival from sudden cardiac arrest. *Annals of Internal Medicine, 164*(1), 23-29.

Background: Survival after sudden cardiac arrest (SCA) remains low, and tools for improved prediction of patients at long-term risk for SCA are lacking. Alternative short-term approaches

aimed at preemptive risk stratification and prevention are needed. Objective: To assess characteristics of symptoms in the 4 weeks before SCA and whether response to these symptoms is associated with better outcomes. Design: Ongoing prospective population-based study. Setting: Northwestern United States (2002 to 2012). Patients: Residents aged 35 to 65 years with SCA. Measurement: Assessment of symptoms in the 4 weeks preceding SCA and association with survival to hospital discharge. Results: Of 839 patients with SCA and comprehensive assessment of symptoms (mean age, 52.6 years [SD, 8]; 75% men), 430 (51%) had warning symptoms (50% of men vs. 53% of women; P = 0.59), mainly chest pain and dyspnea. In most symptomatic patients (93%), symptoms recurred within the 24 hours preceding SCA. Only 81 patients (19%) called emergency medical services (911) to report symptoms before SCA; these persons were more likely to be patients with a history of heart disease (P < 0.001) or continuous chest pain (P < 0.001). Survival when 911 was called in response to symptoms was 32.1% (95% CI, 21.8% to 42.4%) compared with 6.0% (CI, 3.5% to 8.5%) in those who did not call (P < 0.001). Limitation: Potential for recall and response bias, symptom assessment not available in 24% of patients, and missing data for some patients and SCA characteristics. Conclusion: Warning symptoms frequently occur before SCA, but most are ignored. Emergent medical care was associated with survival in patients with symptoms, so new approaches are needed for short-term prevention of SCA. Primary Funding Source: National Heart, Lung, and Blood Institute.

Marshall, L. M., Litwack-Harrison, S., Cawthon, P. M., Kado, D. M., Deyo, R. A., Makris, U. E., et al. (2016). A prospective study of back pain and risk of falls among older community-dwelling women. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences,* BACKGROUND: Back pain and falls are common health conditions among older U.S. women. The extent to which back pain is an independent risk factor for falls has not been established. METHODS: We conducted a prospective study among 6,841 community-dwelling U.S. women at least 65 years of age from the Study of Osteoporotic Fractures (SOF). Baseline questionnaires inquired about any back pain, pain severity, and frequency in the past year. During 1 year of follow-up, falls were summed from self-reports obtained every 4 months. Two outcomes were studied: recurrent falls (>/=2 falls) and any fall (>/=1 fall). Associations of back pain and each

fall outcome were estimated with risk ratios (RRs) and 95% confidence intervals (CIs) from multivariable log-binomial regression. Adjustments were made for age, education, smoking status, fainting history, hip pain, stroke history, vertebral fracture, and Geriatric Depression Scale. RESULTS: Most (61%) women reported any back pain. During follow-up, 10% had recurrent falls and 26% fell at least once. Any back pain relative to no back pain was associated with a 50% increased risk of recurrent falls (multivariable RR = 1.5, 95% CI: 1.3, 1.8). Multivariable RRs for recurrent falls were significantly elevated for all back pain symptoms, ranging from 1.4 (95% CI: 1.1, 1.8) for mild back pain to 1.8 (95% CI: 1.4, 2.3) for activity-limiting back pain. RRs of any fall were also significantly increased albeit smaller than those for recurrent falls. CONCLUSIONS: Older community-dwelling women with a recent history of back pain are at increased risk for falls.

Martin, C. S. (2015). Acupuncture for the prevention and treatment of pediatric perioperative conditions. *Medical Acupuncture, 27*(6), 411-418.

Background: Many pediatric anesthesiologists are interested in multimodal approaches, such as acupuncture, to help manage clinical conditions commonly encountered in the perioperative setting. Methods: A review of the web-based search engine PubMed was conducted to identify research articles that covered the use of acupuncture to prevent or treat perioperative conditions in pediatric patients. Once an article was identified, the reference list of that article was also reviewed to identify additional studies. Results: Sixteen articles were included that investigated the use of acupuncture to prevent or treat four commonly encountered perioperative conditions in children: postoperative nausea and vomiting (PONV), emergence delirium or agitation, acute postoperative pain, and laryngospasm. Articles were excluded if they were not available in English or the specific acupuncture points used were not identified in the article. Acupuncture and acupressure at the Pericardium 6 point were the techniques most often used in studies on the prevention of PONV. However, there was variability in the duration and type of acupuncture or acupressure utilized. Two studies on emergence agitation were included and both reported a decrease in the incidence of agitation, compared to control groups. There is limited data on acute postoperative pain, and includes studies on pain after tonsillectomy and spinal fusion. There are mixed results from two studies on postoperative stridor and laryngospasm. Although many of the

studies reviewed demonstrate the benefit of acupuncture in the perioperative setting, they were often conducted using techniques that could not easily be used in a busy anesthetic practice because of limited time and availability of specialized skills. Thus, the challenge for most clinicians is how to incorporate acupuncture into the daily practice of pediatric anesthesia. Conclusions: There is some evidence to support the use of acupuncture to prevent common perioperative conditions in children. More research is needed to determine the best acupuncture techniques to use for these conditions. © Mary Ann Liebert, Inc. 2015.

Martin, P., Maddocks, K., Leonard, J. P., Ruan, J., Goy, A., Wagner-Johnston, N., et al. (2016). Post-ibrutinib outcomes in patients with mantle cell lymphoma. *Blood,*

Despite unprecedented clinical activity in mantle cell lymphoma (MCL), primary and acquired resistance to ibrutinib is common. The outcomes and ideal management of patients that experience ibrutinib failure are unclear. We performed a retrospective cohort study of all patients with MCL that experienced disease progression while receiving ibrutinib across 15 international sites. Medical records were evaluated for clinical characteristics, pathological, and radiological data, and therapies used pre and post ibrutinib. A total of 114 subjects met eligibility criteria. The median number of prior therapies was 3 (range 0-10). The MIPI scores at start of ibrutinib were low, intermediate, and high in 46%, 31%, and 23%, respectively. Of patients with available data prior to ibrutinib and post-ibrutinib, 34/47 and 11/12 had a Ki67>30%. The median time on ibrutinib was 4.7 months (range 0.7-43.6). The median overall survival (OS) following cessation of ibrutinib was 2.9 months (95% CI 1.6-4.9 months). Of the 104 patients with data available, 73 underwent subsequent treatment an average of 0.3 months after stopping ibrutinib with a median OS of 5.8 months (95% C.I. 3.7 to 10.4 months). Multivariate Cox regression analysis of MIPI prior to post-ibrutinib treatment, and subsequent treatment with bendamustine, cytarabine, or lenalidomide failed to reveal any association with OS. Poor clinical outcomes were noted in the majority of patients with primary or secondary ibrutinib resistance. We could not identify treatments that clearly improved outcomes. Future trials should focus on understanding the mechanisms of ibrutinib resistance and on treatment following ibrutinib.

Martinez-Garcia, M., Campos-Salinas, J., Cabello-Donayre, M., Pineda-Molina, E., Galvez, F. J., Orrego, L. M., et al. (2016). LmABCB3, an atypical mitochondrial ABC transporter essential for leishmania major virulence, acts in heme and cytosolic iron/sulfur clusters biogenesis. *Parasites & Vectors, 9*(1), 7-015-1284-5.

BACKGROUND: Mitochondria play essential biological functions including the synthesis and trafficking of porphyrins and iron/sulfur clusters (ISC), processes that in mammals involve the mitochondrial ATP-Binding Cassette (ABC) transporters ABCB6 and ABCB7, respectively. The mitochondrion of pathogenic protozoan parasites such as Leishmania is a promising goal for new therapeutic approaches. Leishmania infects human macrophages producing the neglected tropical disease known as leishmaniasis. Like most trypanosomatid parasites, Leishmania is auxotrophous for heme and must acquire porphyrins from the host. METHODS: LmABCB3, a new Leishmania major protein with significant sequence similarity to human ABCB6/ABCB7, was identified and characterized using bioinformatic tools. Fluorescent microscopy was used to determine its cellular localization, and its level of expression was modulated by molecular genetic techniques. Intracellular in vitro assays were used to demonstrate its role in amastigotes replication, and an in vivo mouse model was used to analyze its role in virulence. Functional characterization of LmABCB3 was carried out in Leishmania promastigotes and Saccharomyces cerevisiae. Structural analysis of LmABCB3 was performed using molecular modeling software. RESULTS: LmABCB3 is an atypical ABC half-transporter that has a unique N-terminal extension not found in any other known ABC protein. This extension is required to target LmABCB3 to the mitochondrion and includes a potential metal-binding domain. We have shown that LmABCB3 interacts with porphyrins and is required for the mitochondrial synthesis of heme from a host precursor. We also present data supporting a role for LmABCB3 in the biogenesis of cytosolic ISC, essential cofactors for cell viability in all three kingdoms of life. LmABCB3 fully complemented the severe growth defect shown in yeast lacking ATM1, an orthologue of human ABCB7 involved in exporting from the mitochondria a gluthatione-containing compound required for the generation of cytosolic ISC. Indeed, docking analyzes performed with a LmABCB3 structural model using trypanothione, the main thiol in this parasite, as a ligand showed how both, LmABCB3 and yeast ATM1, contain a similar thiol-binding pocket. Additionally, we show solid evidence suggesting that LmABCB3 is an essential gene as dominant negative inhibition of LmABCB3 is lethal for the parasite.

Moreover, the abrogation of only one allele of the gene did not impede promastigote growth in axenic culture but prevented the replication of intracellular amastigotes and the virulence of the parasites in a mouse model of cutaneous leishmaniasis. CONCLUSIONS: Altogether our results present the previously undescribed LmABCB3 as an unusual mitochondrial ABC transporter essential for Leishmania survival through its role in the generation of heme and cytosolic ISC. Hence, LmABCB3 could represent a novel target to combat leishmaniasis.

Mattheij, N. J., Swieringa, F., Mastenbroek, T. G., Berny-Lang, M. A., May, F., Baaten, C. C., et al. (2015). Coated platelets function in platelet-dependent fibrin formation via integrin alphaIIbbeta3 and transglutaminase factor XIII. *Haematologica,*

Coated platelets, formed by collagen and thrombin activation, have been characterized in different ways, i.e. by the formation of a protein coat of alpha-granular proteins, by exposure of procoagulant phosphatidylserine or by high fibrinogen binding. So far, their functional role has remained unclear. Here, we used a novel transglutaminase probe, Rhod-A14, to identify a subpopulation of platelets with a cross-linked protein coat, and compared this with other platelet subpopulations using a panel of functional assays. Platelet stimulation with convulxin/thrombin resulted in initial integrin alphaIIbbeta3 activation, the appearance of a platelet population with high fibrinogen binding - independently of active integrins, but dependent on the presence of thrombin -, followed by phosphatidylserine exposure and binding of factors Va and Xa. A subpopulation of phosphatidylserine-exposing platelets bound Rhod-A14 both in suspension and in thrombi generated on a collagen surface. In suspension, high fibrinogen and Rhod-A14 binding were antagonized by combined inhibition of transglutaminase activity and integrin alphaIIbbeta3. Markedly, in thrombi from mice deficient in transglutaminase factor XIII, platelet-driven fibrin formation and Rhod-A14 binding were abolished by blockage of integrin alphaIIbbeta3. Vice versa, star-like fibrin formation from platelets of a patient with deficiency in alphaIIbbeta3 (Glanzmann thrombasthenia) was abolished upon blockage of transglutaminase activity. We conclude that coated platelets, with initial alphaIIbbeta3 activation and high fibrinogen binding, form a subpopulation of phosphatidylserine-exposing platelets, and function in platelet-dependent star-like fibrin fiber formation via transglutaminase factor XIII and integrin alphaIIbbeta3.

Mehta, P., Potter, C. A., Feinberg, J. H., Simon, J. H., & Maravilla, K. R. (2014). Paresthesias and dysesthesias. (pp. 332-346) Cambridge University Press.

Paresthesias are abnormal sensations in the absence of specific stimuli typically characterized as tingling, prickling, pins and needles, or burning sensations. The symptoms may be transient or persistent and can involve any portion of the body, but most commonly involve the hands, arms, legs, and feet [1]. Paresthesias differ from dysesthesias, which are abnormal interpretations of appropriate stimuli. Dysesthesias often present as a painful sensation and can involve any bodily tissue most commonly the mouth, scalp, skin, or legs [2]. Paresthesias can be caused by a dysfunction or abnormality affecting any level of the somatosensory pathway, with the most common causes affecting peripheral sensory nerves. The somatosensory pathway encompasses multiple types of sensation from the body including light touch, pain, pressure, temperature, and proprioception. However, these modalities are grouped into three different pathways in the spinal cord and have different targets in the brain. Paresthesias represent abnormal impulses from an ectopic focus and can originate from anywhere along the sensory pathway, from the peripheral nerves to the sensory cortex. Any disruption in this pathway can result in altered nerve function and a clinical response [3]. Etiology Paresthesias can be caused by central or peripheral nervous system abnormalities. Disruption can occur in the somatosensory pathway at the level of the peripheral nerve, dorsal root ganglion, dorsal sensory nerve roots, spinal cord or brain. Central nervous system (CNS)-induced paresthesias are most commonly caused by infectious or inflammatory processes, ischemia, structural causes (including tumor or trauma) or degenerative processes (Table 21.1). Peripheral nerve-related paresthesias may be due to a wide variety of etiologies, including entrapment syndromes, traumatic nerve stretch or compression injuries, metabolic disturbances, connective-tissue disorders, autoimmune diseases, vasculitic or inflammatory disorders, toxins, hereditary conditions, malignancy, infections, and nutritional deficiencies (Table 21.2). The focus of this chapter will be on peripheral nerve causes of paresthesias.

Mischler, R. A., Armah, S. M., Wright, B. N., Mattar, S. G., Rosen, A. D., & Gletsu-Miller, N. (2015). Influence of diet and supplements on iron status after gastric bypass surgery. *Surgery for Obesity and Related Diseases : Official Journal of the American Society for Bariatric Surgery,*

BACKGROUND: Iron deficiency is common after Roux-en-Y gastric bypass (RYGB) surgery, but there is no consensus on the optimal diet quality and quantity for restoring and preserving iron status. OBJECTIVES: The authors explored the impact of dietary and supplemental sources of iron and absorptive factors on iron status. SETTING: Academic, United States. METHODS: In a cross-sectional cohort of individuals who underwent RYGB, nutrient intakes from food and supplements were measured using 3-day food records. Blood biomarkers of iron status, including concentrations of ferritin, total iron binding capacity, serum transferrin receptor (sTfR), and the sTfR:ferritin ratio, were assessed by a reference laboratory; iron deficiency was defined as having at least 2 abnormal measures. Associations between iron status biomarkers and dietary predictors were determined using regression analysis. RESULTS: Of the 36 participants, 97% were female, the mean age was 45 years (95% confidence interval, 41-48 years), and body mass index was 32 (30-35) kg/m2. Iron deficiency was found in 42% of participants. Dietary intake of heme iron, found in meats, was favorably associated with 3 iron status biomarkers (ferritin, beta = .366; sTfR:ferritin ratio, beta = -.459; and total iron binding capacity, beta = -18.26; all P<.05), independent of obesity-induced inflammation. Intake of vitamin C from food contributed to iron status (ferritin, beta = .010 and sTfR:ferritin ratio, beta = -.011; P<.05). Use of supplementary non-heme iron, at doses recommended for prophylaxis (45 mg/d), was positively associated with serum ferritin (beta = .964; P = .029). CONCLUSIONS: For patients who have undergone RYGB, consuming high, but realistic amounts of heme iron in meat, vitamin C from food, and adherence to recommended iron supplements can prevent iron deficiency.

Mithal, P., Howard, L. E., Aronson, W. J., Terris, M. K., Cooperberg, M. R., Kane, C. J., et al. (2016). Positive surgical margins in radical prostatectomy patients do not predict long-term oncological outcomes: Results from the shared equal access regional cancer hospital (SEARCH) cohort. *BJU International, 117*(2), 244-248.

Objective To assess the impact of positive surgical margins (PSMs) on long-term outcomes after radical prostatectomy (RP), including metastasis, castrate-resistant prostate cancer (CRPC), and prostate cancer-specific mortality (PCSM). Patients and Methods Retrospective study of 4 051 men in the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort treated by RP from 1988 to 2013. Proportional hazard models were used to estimate hazard ratios (HRs) of PSMs in

predicting biochemical recurrence (BCR), CRPC, metastases, and PCSM. To determine if PSMs were more predictive in certain patients, analyses were stratified by pathological Gleason score, stage, and preoperative prostate-specific antigen (PSA) level. Results The median (interquartile range) follow-up was 6.6 (3.2-10.6) years and 1 127 patients had >10 years of follow-up. During this time, 302 (32%) men had BCR, 112 (3%) developed CRPC, 144 (4%) developed metastases, and 83 (2%) died from prostate cancer. There were 1 600 (40%) men with PSMs. In unadjusted models, PSMs were significantly associated with all adverse outcomes: BCR, CRPC, metastases and PCSM (all P ≤ 0.001). After adjusting for demographic and pathological characteristics, PSMs were associated with increased risk of only BCR (HR 1.98, P 0.18). Similar results were seen when stratified by pathological Gleason score, stage, or PSA level, and when patients who underwent adjuvant radiotherapy were excluded. Conclusions PSMs after RP are not an independent risk factor for CRPC, metastasis, or PCSM overall or within any subset. In the absence of other high-risk features, PSMs alone may not be an indication for adjuvant radiotherapy.

Moal, B., Lafage, V., Smith, J. S., Ames, C. P., Mundis, G., Terran, J. S., et al. (2015). Clinical improvement through surgery for adult spinal deformity: What can be expected and who is likely to benefit most? *Spine Deformity, 3*(6), 566-574.

Study Design Multicenter, prospective, nonconsecutive, surgical case series from the International Spine Study Group. Objectives To evaluate the extent of clinical improvement after surgery for adult spinal deformity (ASD) based on minimal clinically important difference (MCID) and baseline measures. Summary of Background Data For ASD, evaluation of surgical treatment success using clinical scores should take into account baseline disability and pain and the improvement defined relative to the MCID. Methods Inclusion criteria included operative patients (age >18 years) with baseline and 2-year SRS-22 scores. Normative values for the SRS scores were included and improvement for patients was expressed in number of MCIDs. At baseline, patients were classified by differences in activity and pain scores from normative values in four groups: "worst," "severe," "poor," and, "moderate." At 2 years after surgery, patients were classified into four groups based on their change in SRS score as follows: "no improvement or deterioration," "mediocre," "satisfactory," or "optimal." Distinction among curve types was also

performed based on the SRS-Schwab ASD classification. Results A total of 223 patients (age = 55 ± 15 years) were included. At baseline, for 77% of the patients, the worst scores were in Activity or Pain. At baseline, the distribution was 36% "worst," 28% "severe," 19% "poor," and 17% "moderate." Patients with sagittal malalignment only were more likely to be in the "worst" state (54%). The overall distribution of improvement was as follows: 24% no improvement or deterioration, 17% mediocre, 25% satisfactory, and 33% optimal. Forty-one percent of baseline "moderate" patients achieved no improvement. Of the baseline "worst" patients, 20% achieved no improvement, and 36% and 19% achieved "satisfactory" and "optimal" improvement, respectively. Conclusion Overall, 24% of patients did not experience improvement after surgery. Patients with baseline severe disability were more likely to perceive improvement than patients with less disability. Level of Evidence Level II. © 2015 Scoliosis Research Society.

Moghadamfalahi, M., Orhan, U., Akcakaya, M., Nezamfar, H., Fried-Oken, M., & Erdogmus, D. (2015). Language-model assisted brain computer interface for typing: A comparison of matrix and rapid serial visual presentation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering, 23*(5), 910-920.

Noninvasive electroencephalography (EEG)-based brain-computer interfaces (BCIs) popularly utilize event-related potential (ERP) for intent detection. Specifically, for EEG-based BCI typing systems, different symbol presentation paradigms have been utilized to induce ERPs. In this manuscript, through an experimental study, we assess the speed, recorded signal quality, and system accuracy of a language-model-Assisted BCI typing system using three different presentation paradigms: A 4 7 matrix paradigm of a 28-character alphabet with row-column presentation (RCP) and single-character presentation (SCP), and rapid serial visual presentation (RSVP) of the same. Our analyses show that signal quality and classification accuracy are comparable between the two visual stimulus presentation paradigms. In addition, we observe that while the matrix-based paradigm can be generally employed with lower inter-Trial-interval (ITI) values, the best presentation paradigm and ITI value configuration is user dependent. This potentially warrants offering both presentation paradigms and variable ITI options to users of BCI typing systems.

Moini, A., Nikoozadeh, A., Choe, J. W., Khuri-Yakub, B. T., Chang, C., Stephens, D., et al. (2015). Fabrication, packaging, and catheter assembly of 2D CMUT arrays for endoscopic ultrasound and cardiac imaging. *ASME 2015 International Technical Conference and Exhibition on Packaging and Integration of Electronic and Photonic Microsystems, InterPACK 2015, collocated with the ASME 2015 13th International Conference on Nanochannels, Microchannels, and Minichannels, , 3.*

Ultrasound is increasingly in demand as a medical imaging tool and can be particularly beneficial in the field of intracardiac echocardiography (ICE). However, many challenges remain in the development of a 3D ultrasound imaging system. We have designed and fabricated a quad-ring capacitive micromachined ultrasound transducer (CMUT) for real-time, volumetric medical imaging. Each CMUT array is composed of four concentric, independent ring arrays, each operating at a different frequency, with 128 elements per ring. In this project, one ring will be used for imaging. A large (5mm diameter) lumen is available for delivering other devices, including high intensity focused ultrasound transducers for therapeutic applications or optical fibers for photoacoustic imaging. We address several challenges in developing a 3D imaging system. Through wafer vias are incorporated in the fabrication process for producing 2D CMUT arrays. Device integration with electronics is achieved through solder bumping the arrays, designing a flexible PCB, and flip chip bonding CMUT and ASICs to the flexible substrate. Finally, we describe a method for integrating the flex assembly into a catheter shaft. The package, once assembled, will be used for in-vivo open chest experiments. Copyright © 2015 by ASME.

Morgan, T. K. (2015). Role of the placenta in preterm birth: A review. *American Journal of Perinatology,*

Preterm birth is a multifactorial syndrome with a variety of risk factors and long-term health consequences for the child. Placental pathology provides important diagnostic information to ascertain the cause of preterm birth. For example, intra-amniotic infection is one risk factor, but accumulating evidence based on placental pathology, amniotic fluid cultures, and polymerase chain reaction studies suggests infection may be a less common cause of preterm birth than previously suspected, especially after 32 weeks' gestation. Instead, many cases of spontaneous preterm labor leading to preterm birth appear to be caused by placental insufficiency, similar to preeclampsia and fetal growth restriction. Other causes of preterm birth, including retroplacental

abruption, chronic villitis, and twin gestations, also have specific placental pathology related to placental insufficiency. New insights into the underlying mechanisms regulating uteroplacental blood flow and the impact of placental malperfusion on placental health may lead to improved early gestation diagnostic testing and a revolution in preventative care for both the mother and her child. Copyright © 2015, Thieme Medical Publishers. All rights reserved.

Morgan, T. K. (2016). Role of the placenta in preterm birth: A review. *American Journal of Perinatology,*

Preterm birth is a multifactorial syndrome with a variety of risk factors and long-term health consequences for the child. Placental pathology provides important diagnostic information to ascertain the cause of preterm birth. For example, intra-amniotic infection is one risk factor, but accumulating evidence based on placental pathology, amniotic fluid cultures, and polymerase chain reaction studies suggests infection may be a less common cause of preterm birth than previously suspected, especially after 32 weeks' gestation. Instead, many cases of spontaneous preterm labor leading to preterm birth appear to be caused by placental insufficiency, similar to preeclampsia and fetal growth restriction. Other causes of preterm birth, including retroplacental abruption, chronic villitis, and twin gestations, also have specific placental pathology related to placental insufficiency. New insights into the underlying mechanisms regulating uteroplacental blood flow and the impact of placental malperfusion on placental health may lead to improved early gestation diagnostic testing and a revolution in preventative care for both the mother and her child.

Mukherjee, S., Walter, S., Kauwe, J. S. K., Saykin, A. J., Bennett, D. A., Larson, E. B., et al. (2015). Genetically predicted body mass index and alzheimer's disease-related phenotypes in three large samples: Mendelian randomization analyses. *Alzheimer's and Dementia, 11*(12), 1439-1451.

Observational research shows that higher body mass index (BMI) increases Alzheimer's disease (AD) risk, but it is unclear whether this association is causal. We applied genetic variants that predict BMI in Mendelian randomization analyses, an approach that is not biased by reverse causation or confounding, to evaluate whether higher BMI increases AD risk. We evaluated individual-level data from the AD Genetics Consortium (ADGC: 10,079 AD cases and 9613

controls), the Health and Retirement Study (HRS: 8403 participants with algorithm-predicted dementia status), and published associations from the Genetic and Environmental Risk for AD consortium (GERAD1: 3177 AD cases and 7277 controls). No evidence from individual single-nucleotide polymorphisms or polygenic scores indicated BMI increased AD risk. Mendelian randomization effect estimates per BMI point (95% confidence intervals) were as follows: ADGC, odds ratio (OR) = 0.95 (0.90-1.01); HRS, OR = 1.00 (0.75-1.32); GERAD1, OR = 0.96 (0.87-1.07). One subscore (cellular processes not otherwise specified) unexpectedly predicted lower AD risk. © 2015 The Alzheimer's Association.

Myatt, L., & Maloyan, A. (2016). Obesity and placental function. *Seminars in Reproductive Medicine, 34*(1), 42-49.

An increasing number of women of reproductive age are obese which affects the continuum of pregnancy and is associated with an increased incidence of adverse maternal and fetal outcomes, including preeclampsia, preterm birth, stillbirth, congenital anomalies, and macrosomia. Maternal obesity is associated with an increased incidence of metabolic and cardiovascular disease later in life in the mother and in the offspring who are developmentally programed by the obese pregnancy environment. The placenta transduces and mediates the effect of the adverse maternal environment to the fetus. The obese maternal environment is characterized by hyperlipidemia and an exaggerated state of inflammation and oxidative stress compared with normal pregnancy. Heightened inflammation and oxidative/nitrative stress are found in the placenta in association with placental dysfunction. We have described reduced mitochondrial respiration and ATP generation in trophoblast isolated from placentas of obese compared with lean women, again suggesting compromised placental function. In utero development exhibits sexual dimorphism with the male fetus at greater risk of poor outcome. We have shown dimorphism in inflammation-mediated regulation of trophoblast mitochondrial respiration. There is also increasing evidence that the obese in utero environment may cause epigenetic changes in placenta leading to altered function.

Nabavizadeh, N., Burt, L. M., Mancini, B. R., Morris, Z. S., Walker, A. J., Miller, S. M., et al. (2016). Results of the 2013-2015 association of residents in radiation oncology survey of chief residents

in the united states. *International Journal of Radiation Oncology Biology Physics, 94*(2), 228-234.

Purpose The purpose of this project was to survey radiation oncology chief residents to define their residency experience and readiness for independent practice. Methods and Materials During the academic years 2013 to 2014 and 2014 to 2015, the Association of Residents in Radiation Oncology (ARRO) conducted an electronic survey of post-graduate year-5 radiation oncology residents in the United States during the final 3 months of training. Descriptive statistics are reported. Results Sixty-six chief residents completed the survey in 2013 to 2014 (53% response rate), and 69 completed the survey in 2014 to 2015 (64% response rate). Forty to 85% percent of residents reported inadequate exposure to high-dose rate and low-dose rate brachytherapy. Nearly all residents in both years (>90%) reported adequate clinical experience for the following disease sites: breast, central nervous system, gastrointestinal, genitourinary, head and neck, and lung. However, as few as 56% reported adequate experience in lymphoma or pediatric malignancies. More than 90% of residents had participated in retrospective research projects, with 20% conducting resident-led prospective clinical trials and 50% conducting basic science or translational projects. Most chief residents reported working 60 or fewer hours per week in the clinical/hospital setting and performing fewer than 15 hours per week tasks that were considered to have little or no educational value. There was more than 80% compliance with Accreditation Council for Graduate Medical Education (ACGME) work hour limits. Fifty-five percent of graduating residents intended to join an established private practice group, compared to 25% who headed for academia. Residents perceive the job market to be more competitive than previous years. Conclusions This first update of the ARRO chief resident survey since the 2007 to 2008 academic year documents US radiation oncology residents' experiences and conditions over a 2-year period. This analysis may serve as a valuable tool for those seeking to improve training of the next generation of oncology leaders. © 2016 Elsevier Inc.

Nabozny, M. J., Kruser, J. M., Steffens, N. M., Brasel, K. J., Campbell, T. C., Gaines, M. E., et al. (2016). Constructing high-stakes surgical decisions: It's better to die trying. *Annals of Surgery, 263*(1), 64-70.

Objective: To explore high-stakes surgical decision making from the perspective of seniors and surgeons. Background: A majority of older chronically ill patients would decline a low-risk

procedure if the outcome was severe functional impairment. However, 25% of Medicare beneficiaries have surgery in their last 3 months of life, which may be inconsistent with their preferences. How patients make decisions to have surgery may contribute to this problem of unwanted care. Methods: We convened 4 focus groups at senior centers and 2 groups of surgeons in Madison and Milwaukee, Wisconsin, where we showed a video about a decision regarding a choice between surgery and palliative care. We used qualitative content analysis to identify themes about communication and explanatory models for end-of-life treatment decisions. Results: Seniors (n=37) and surgeons (n=17) agreed that maximizing quality of life should guide treatment decisions for older patients. However, when faced with an acute choice between surgery and palliative care, seniors viewed this either as a choice between life and death or a decision about how to die. Although surgeons agreed that very frail patients should not have surgery, they held conflicting views about presenting treatment options. Conclusions: Seniors and surgeons highly value quality of life, but this notion is difficult to incorporate in acute surgical decisions. Some seniors use these values to consider a choice between surgery and palliative care, whereas others view this as a simple choice between life and death. Surgeons acknowledge challenges framing decisions and describe a clinical momentum that promotes surgical intervention.

Nabozny, M. J., Kruser, J. M., Steffens, N. M., Pecanac, K. E., Brasel, K. J., Chittenden, E. H., et al. (2016). Patient-reported limitations to surgical buy-in: A qualitative study of patients facing high-risk surgery. *Annals of Surgery,*

OBJECTIVE: To characterize how patients buy-in to treatments beyond the operating room and what limits they would place on additional life-supporting treatments. BACKGROUND: During a high-risk operation, surgeons generally assume that patients buy-in to life-supporting interventions that might be necessary postoperatively. How patients understand this agreement and their willingness to participate in additional treatment is unknown. METHODS: We purposively sampled surgeons in Toronto, Ontario, Boston, Massachusetts, and Madison, Wisconsin, who are good communicators and routinely perform high-risk operations. We audio-recorded their conversations with patients considering high-risk surgery. For patients who were then scheduled for surgery, we performed open-ended preoperative and postoperative

interviews. We used directed qualitative content analysis to analyze the interviews and surgeon visits, specifically evaluating the content about the use of postoperative life support. RESULTS: We recorded 43 patients' conversations with surgeons, 34 preoperative, and 27 postoperative interviews. Patients expressed trust in their surgeon to make decisions about additional treatments if a serious complication occurred, yet expressed a preference for significant treatment limitations that were not discussed with their surgeon preoperatively. Patients valued the existence or creation of an advance directive preoperatively, but they did not discuss this directive with their surgeon. Instead they assumed it would be effective if needed and that family members knew their wishes. CONCLUSIONS: Patients implicitly trust their surgeons to treat postoperative complications as they arise. Although patients may buy-in to some additional postoperative interventions, they hold a broad range of preferences for treatment limitations that were not discussed with the surgeon preoperatively.

Nagel, C., Beach, J., Iribagiza, C., & Thomas, E. A. (2015). Evaluating cellular instrumentation on rural handpumps to improve service delivery-A longitudinal study in rural rwanda. *Environmental Science and Technology, 49*(24), 14292-14300.

In rural sub-Saharan Africa, where handpumps are common, 10-67% are nonfunctional at any one time, and many never get repaired. Increased reliability requires improved monitoring and responsiveness of maintenance providers. In 2014, 181 cellular enabled water pump use sensors were installed in three provinces of Rwanda. In three arms, the nominal maintenance model was compared against a "best practice" circuit rider model, and an "ambulance" service model. In only the ambulance model was the sensor data available to the implementer, and used to dispatch technicians. The study ran for seven months in 2014-2015. In the study period, the nominal maintenance group had a median time to successful repair of approximately 152 days, with a mean per-pump functionality of about 68%. In the circuit rider group, the median time to successful repair was nearly 57 days, with a per-pump functionality mean of nearly 73%. In the ambulance service group, the successful repair interval was nearly 21 days with a functionality mean of nearly 91%. An indicative cost analysis suggests that the cost per functional pump per year is approximately similar between the three models. However, the benefits of reliable water

service may justify greater focus on servicing models over installation models. © 2015 American Chemical Society.

Nakayama, S., Amiry-Moghaddam, M., Ottersen, O. P., & Bhardwaj, A. (2016). Conivaptan, a selective arginine vasopressin V and V receptor antagonist attenuates global cerebral edema following experimental cardiac arrest via perivascular pool of aquaporin-4. *Neurocritical Care,* BACKGROUND: Cerebral edema is a major cause of mortality following cardiac arrest (CA) and cardiopulmonary resuscitation (CPR). Arginine vasopressin (AVP) and water channel aquaporin-4 (AQP4) have been implicated in the pathogenesis of CA-evoked cerebral edema. In this study, we examined if conivaptan, a V1a and V2 antagonist, attenuates cerebral edema following CA/CPR in wild type (WT) mice as well as mice with targeted disruption of the gene encoding alpha-syntrophin (alpha-syn-/-) that demonstrate diminished perivascular AQP4 pool. METHODS: Isoflurane-anesthetized adult male WT C57Bl/6 and alpha-syn-/- mice were subjected to 8 min CA/CPR and treated with either bolus IV injection (0.15 or 0.3 mg/kg) followed by continuous infusion of conivaptan (0.15 mg/kg/day or 0.3 mg/kg/day), or vehicle infusion for 48 h. Serum osmolality, regional brain water content, and blood-brain barrier (BBB) disruption were determined at the end of the experiment. Sham-operated mice in both strains served as controls. RESULTS: Treatment with conivaptan elevated serum osmolality in a dose-dependent manner. In WT mice, conivaptan at 0.3 mg dose significantly attenuated regional water content in the caudoputamen (81.0 +/- 0.5 vs 82.5 +/- 0.4 % in controls; mean +/- SEM) and cortex (78.8 +/- 0.2 vs 79.4 +/- 0.2 % in controls), while conivaptan at 0.15 mg was not effective. In alpha-syn-/- mice, conivaptan at 0.3 mg dose did not attenuate water content compared with controls. Conivaptan (0.3 mg/kg/day) attenuated post-CA BBB disruption at 48 h in WT mice but not in alpha-syn-/- mice. CONCLUSIONS: Continuous IV infusion of conivaptan attenuates cerebral edema and BBB disruption following CA. These effects of conivaptan that are dependent on the presence of perivascular pool of AQP4 appear be mediated via its dual effect on V1 and V2 receptors.

Narala, R., Scarinci, F., Shaarawy, A., Simonett, J. M., Flaxel, C. J., & Fawzi, A. A. (2016). Longitudinal quantitative evaluation of photoreceptor volume following repair of macula-off retinal

detachment. *Retina (Philadelphia, Pa.),*

PURPOSE: To quantify photoreceptor volume changes after successful surgical repair of macula-off retinal detachment and to correlate these volumetric changes to postoperative best-corrected visual acuity (BCVA). METHODS: Retrospective study of 15 eyes of 15 patients with macula-off retinal detachment who underwent successful surgical repair. A minimum of 4 optical coherence tomography scans that straddled the foveal center was used to quantify the central photoreceptor volume (central 1 mm). RESULTS: Mean photoreceptor volume at the first postoperative visit was 0.451 mm, increasing to 0.523 mm at the final postoperative visit (P = 0.004). Mean BCVA improved from 1.13 +/- 0.59 logarithm of the minimum angle of resolution units (approximately 20/270) preoperatively to 0.52 +/- 0.42 logarithm of the minimum angle of resolution units (approximately 20/66) at the final postoperative visit (P = 0.001). Mean photoreceptor volume at either the initial or final visit demonstrated significant correlations with final postoperative BCVA (r = -0.670, P = 0.017 and r = -0.753, P = 0.005, respectively). Shorter time interval from diagnosis to surgery was significantly associated with greater mean final postoperative photoreceptor volume (r = -0.588, P = 0.021) and better mean final postoperative BCVA (r = 0.709, P = 0.003). CONCLUSION: We observed a significant increase in photoreceptor volume after successful retinal detachment repair; photoreceptor volume was positively associated with BCVA and time to surgery. Our series emphasizes the importance of prompt surgical repair and shows that photoreceptor recovery and volumetric improvement correlate significantly with BCVA.

Naugler, W. E., & Karin, M. (2015). NF-κB and cancer. (pp. 336-352) Cambridge University Press.

Introduction Nuclear factor-κB (NF-κB) transcription factors and their signaling pathways have come to the forefront of the cancer field as mechanistic links connecting chronic inflammation and oncogenesis (1). These master transcription factors integrate multiple stimuli and co-ordinate innate and adaptive immune responses involved in acute and chronic inflammation (2). Epidemiological studies which pointed out that chronic inflammation and persistent infections greatly increase the risk of cancers of stomach, colon, and liver first suggested a link between inflammation, the innate immune response, and cancer (3). NF-κB was suggested as the molecular culprit that bridges these pathophysiological states and responses (1). However,

establishing the association between NF-κB signaling and oncogenesis has been a challenging task because NF-κB and its activating machinery are rarely mutated in cancer cells in the same way as classical oncogenes (like Ras) or tumor-suppressor genes (like p53). Nonetheless, much evidence has been gathered, both through correlative studies and through direct experimentation, that NF-κB signaling does indeed contribute to cancer development and progression, mainly in inflammation-associated cancers, but also in cancers where underlying chronic inflammation plays little or no role (for example, breast and prostate cancers). The list of human cancers that were found to exhibit constitutive NF-κB activation is long (see Table 29.1). Experimental evidence providing causality for NF-κB signaling in oncogenesis has accumulated over the past several years (4), and will be detailed in this chapter. © Cambridge University Press 2014.

Nechiporuk, T., McGann, J., Mullendorff, K., Hsieh, J., Wurst, W., Floss, T., et al. (2016). The REST remodeling complex protects genomic integrity during embryonic neurogenesis. *Elife, 5*, 10.7554/eLife.09584.

The timely transition from neural progenitor to post-mitotic neuron requires down-regulation and loss of the neuronal transcriptional repressor, REST. Here, we have used mice containing a gene trap in the Rest gene, eliminating transcription from all coding exons, to remove REST prematurely from neural progenitors. We find that catastrophic DNA damage occurs during S-phase of the cell cycle, with long-term consequences including abnormal chromosome separation, apoptosis, and smaller brains. Persistent effects are evident by latent appearance of proneural glioblastoma in adult mice deleted additionally for the tumor suppressor p53 protein (p53). A previous line of mice deleted for REST in progenitors by conventional gene targeting does not exhibit these phenotypes, likely due to a remaining C-terminal peptide that still binds chromatin and recruits co-repressors. Our results suggest that REST-mediated chromatin remodeling is required in neural progenitors for proper S-phase dynamics, as part of its well-established role in repressing neuronal genes until terminal differentiation.

Nelson, A. M. (2016). Less than 5 minutes. *Annals of Emergency Medicine, 67*(2), 286-287.

Newgard, C. D., Fu, R., Zive, D., Rea, T., Malveau, S., Daya, M., et al. (2015). Prospective validation of the national field triage guidelines for identifying seriously injured persons. *Journal of the American College of Surgeons,*

Background: The national field trauma triage guidelines have been widely implemented in US trauma systems, but never prospectively validated. We sought to prospectively validate the guidelines, as applied by out-of-hospital providers, for identifying high-risk trauma patients. Study Design: This was an out-of-hospital prospective cohort study from January 1, 2011 through December 31, 2011 with 44 Emergency Medical Services agencies in 7 counties in 2 states. We enrolled injured patients transported to 28 acute care hospitals, including 7 major trauma centers (Level I and II trauma hospitals) and 21 nontrauma hospitals. The primary exposure term was Emergency Medical Services' use of one or more field triage criteria in the national field triage guidelines. Outcomes included Injured Severity Score ≥16 (primary) and critical resource use within 24 hours of emergency department arrival (secondary). Results: We enrolled 53,487 injured children and adults transported by Emergency Medical Services to an acute care hospital, 17,633 of which were sampled for the primary analysis; 13.9% met field triage guidelines, 3.1% had Injury Severity Score ≥16, and 1.7% required early critical resources. The sensitivity and specificity of the field triage guidelines were 66.2% (95% CI, 60.2-71.7%) and 87.8% (95% CI, 87.7-88.0%) for Injury Severity Score ≥16 and 80.1% (95% CI, 65.8-89.4%) and 87.3% (95% CI 87.1-87.4%) for early critical resource use. Triage guideline sensitivity decreased with age, from 87.4% in children to 51.8% in older adults. Conclusions: The national field triage guidelines are relatively insensitive for identifying seriously injured patients and patients requiring early critical interventions, particularly among older adults. © 2016 American College of Surgeons.

Newgard, C. D., Holmes, J. F., Haukoos, J. S., Bulger, E. M., Staudenmayer, K., Wittwer, L., et al. (2016). Improving early identification of the high-risk elderly trauma patient by emergency medical services. *Injury, 47*(1), 19-25.

Study objective We sought to (1) define the high-risk elderly trauma patient based on prognostic differences associated with different injury patterns and (2) derive alternative field trauma triage guidelines that mesh with national field triage guidelines to improve identification of high-risk

elderly patients. Methods This was a retrospective cohort study of injured adults ≥65 years transported by 94 EMS agencies to 122 hospitals in 7 regions from 1/1/2006 through 12/31/2008. We tracked current field triage practices by EMS, patient demographics, out-of-hospital physiology, procedures and mechanism of injury. Outcomes included Injury Severity Score ≥ 16 and specific anatomic patterns of serious injury using abbreviated injury scale score ≥3 and surgical interventions. In-hospital mortality was used as a measure of prognosis for different injury patterns. Results 33,298 injured elderly patients were transported by EMS, including 4.5% with ISS ≥ 16, 4.8% with serious brain injury, 3.4% with serious chest injury, 1.6% with serious abdominal-pelvic injury and 29.2% with serious extremity injury. In-hospital mortality ranged from 18.7% (95% CI 16.7-20.7) for ISS ≥ 16 to 2.9% (95% CI 2.6-3.3) for serious extremity injury. The alternative triage guidelines (any positive criterion from the current guidelines, GCS ≤ 14 or abnormal vital signs) outperformed current field triage practices for identifying patients with ISS ≥ 16: sensitivity (92.1% [95% CI 89.6-94.1%] vs. 75.9% [95% CI 72.3-79.2%]), specificity (41.5% [95% CI 40.6-42.4%] vs. 77.8% [95% CI 77.1-78.5%]). Sensitivity decreased for individual injury patterns, but was higher than current triage practices. Conclusions High-risk elderly trauma patients can be defined by ISS ≥ 16 or specific non-extremity injury patterns. The field triage guidelines could be improved to better identify high-risk elderly trauma patients by EMS, with a reduction in triage specificity.

Nezhat, F. R., Kolev, T., & Pejovic, T. (2015). Laparoscopic and robotic procedures. (pp. 611-647) Cambridge University Press.

Introduction Gynecological applications of laparoscopy have contributed greatly to the popularization of laparoscopic surgery. Laparoscopic gynecological surgery has many accepted applications, from diagnostic use to facilitation of hysteroscopy and reconstructive pelvic surgery. According to the American Association of Gynecological Laparoscopists survey of members regarding patterns in the use of laparoscopic procedures, diagnostic laparoscopy was the most commonly performed laparoscopic procedure. Indications for laparoscopy The main indications for diagnostic gynecological laparoscopy include infertility, pelvic pain, pelvic inflammatory disease, suspected pelvic masses, and ectopic pregnancy. The evaluation of pelvic pain and infertility

focuses on identification of endometriosis, adhesions, or tubal blockage. Less common indications for minimally invasive procedures (laparoscopy) include evaluation of possible uterine perforation during dilatation and curettage, evaluation of early postoperative complications, removal of foreign bodies, and evaluation of pelvic tumors before laparotomy. The workup prior to performing diagnostic laparoscopy for acute pelvic pain should include documentation of the location, severity and duration of symptoms, last menstrual period, pregnancy test, urinanalysis, and complete blood count. Adhesiolysis Peritoneal adhesions may cause pelvic pain, infertility, and bowel obstruction. Formation of intra-abdominal adhesions between the operative scar and the underlying viscera is a common consequence of laparotomy. Patients with midline incisions have more adhesions than those with Pfannenstiel incisions.

Nguyen, K., Teruya, T., Alabi, O., Sheng, N., Bianchi, C., Chiriano, J., et al. (2016). Comparison of non-penetrating titanium clips versus continuous polypropylene suture in dialysis access creation. *Annals of Vascular Surgery,*

INTRODUCTION AND OBJECTIVES: Non-penetrating titanium surgical clips (clips) offer a theoretical advantage of inducing less intimal hyperplasia at an anastomosis due to less endothelial injury. Whether this translates into improved outcomes when used in the creation of arteriovenous fistulas (AVF) remains unclear. We sought to compare the maturation, patency and failure rates of anastomoses created using traditional continuous polypropylene suture and clips. METHODS: All primary AVF created at a single Veterans Administration medical center were reviewed over a 6 year period. Anastomoses were created with either clips or suture based on surgeon preference. Patient characteristics and surgical outcomes were collected. Comparisons were made between the two groups. RESULTS: Over a six-year period, 334 fistulas were created (29% suture and 71% clips) in 326 patients. The mean age was 64.8+/-11 years with 98% males. Comorbidities included diabetes (70%), hypertension (96.1%), and tobacco use (52.9% previous or current). Approximately half the patients were pre-dialysis. Comparison of patient characteristics showed no differences between the suture and clip groups. There was no significant difference in maturation rate (suture 79% vs. clips 72%, P=.25), median time to maturation (suture 62+/-35 vs. clips 71+/-13 days, P=.07), 1 year primary patency rate (suture 37.4% vs. clips 39.6, P=.72), 1 year assisted primary patency rate (suture 82.4% vs. clips

76.3%, P=.31), or overall failure rates (suture 62% vs. clips 58%, P=.56). Median time to initial failure or re-intervention was not significantly different in the clip group (suture 615 [range 239 to 991] vs. clips 812 [range 635 to 989] days, P=.72). CONCLUSIONS: Compared to traditional polypropylene suture creation of upper extremity arteriovenous fistulas, non-penetrating clips had equivalent maturation, 1 year patency and overall failure rates. Neither clips nor suture offer any clear advantage in the creation of arteriovenous fistulas.

Nickerson, A., Huang, T., Lin, L. -., & Nan, X. (2015). Photoactivated localization microscopy with bimolecular fluorescence complementation (bifc-palm). *Journal of Visualized Experiments, 2015*(106)

Protein-protein interactions (PPIs) are key molecular events to biology. However, it remains a challenge to visualize PPIs with sufficient resolution and sensitivity in cells because the resolution of conventional light microscopy is diffraction-limited to ~250 nm. By combining bimolecular fluorescence complementation (BiFC) with photoactivated localization microscopy (PALM), PPIs can be visualized in cells with single molecule sensitivity and nanometer spatial resolution. BiFC is a commonly used technique for visualizing PPIs with fluorescence contrast, which involves splitting of a fluorescent protein into two non-fluorescent fragments. PALM is a recent superresolution microscopy technique for imaging biological samples at the nanometer and single molecule scales, which uses phototransformable fluorescent probes such as photoactivatable fluorescent proteins (PA-FPs). BiFC-PALM was demonstrated by splitting PAmCherry1, a PA-FP compatible with PALM, for its monomeric nature, good single molecule brightness, high contrast ratio, and utility for stoichiometry measurements. When split between amino acids 159 and 160, PAmCherry1 can be made into a BiFC probe that reconstitutes efficiently at 37 °C with high specificity to PPIs and low non-specific reconstitution. Ras-Raf interaction is used as an example to show how BiFC-PALM helps to probe interactions at the nanometer scale and with single molecule resolution. Their diffusion can also be tracked in live cells using single molecule tracking (smt-) PALM. In this protocol, factors to consider when designing the fusion proteins for BiFC-PALM are discussed, sample preparation, image acquisition, and data analysis steps are explained, and a few exemplary results are showcased. Providing high spatial resolution,

specificity, and sensitivity, BiFC-PALM is a useful tool for studying PPIs in intact biological samples. © 2015 Journal of Visualized Experiments.

Nigg, J. T. (2016). Where do epigenetics and developmental origins take the field of developmental psychopathology? *Journal of Abnormal Child Psychology,*

The time is ripe for upgrading or rethinking the assumed paradigms for how we study developmental psychopathology. The classic transactional models appear robust but need specification in terms of biological and psychosocial processes. That specification is increasingly tractable due to developments in genetics, epigenetics, the measurement of psychosocial processes, and theory and data on developmental origins of health and disease. This essay offers a high-level view of where the field has been and where it may be going in regard to nosology and conceptions of etiology. Remarks seek to consider rapidly evolving contexts not only for children, but also for the science itself due to progress in our field and in neighboring fields. Illustrations are provided as to how syndromal nosology can be enriched and advanced by careful integration with biologically relevant behavioral dimensions and application of quantitative methods. It is concluded that a revised, forward-looking, transactional model of abnormal child psychology will incorporate prenatal and postnatal developmental programming, epigenetic mechanisms and their associated genotype x environment interactions, and inflammatory processes as a potential common mediator influencing numerous health and mental health conditions.

Nigg, J. T., Johnstone, J. M., Musser, E. D., Long, H. G., Willoughby, M., & Shannon, J. (2016). Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: New data and meta-analysis. *Clinical Psychology Review, 43*, 67-79.

Background: Literature has suggested that ADHD may be associated with increased risk of obesity. If so, this would have important clinical implications. Objective: To clarify the size of the association between ADHD and obesity and to evaluate key moderators of the association including medication, gender, age, and psychiatric comorbidity. Method: Two preliminary studies are presented to supply critical additional data for the meta-analysis: a two-year longitudinal study of an ADHD case-control sample of 313 children aged 7-11, and a national survey study of

45,309 families in the United States using the 2012 National Survey of Children's Health. Formal meta-analysis was then conducted. The identification procedure yielded 43 studies, reporting 225 comparisons or effect sizes, studying 703,937 participants An overall effect size was estimated with a random effects model (after pooling within study using a modified fixed effects model). Effect size was then examined in relation to medication, gender, age, and psychiatric comorbidity. Results: The new study of children revealed no reliable association of ADHD and body mass index at any age or time point. In the national survey, ADHD was associated with obesity only in adolescent girls but not in children or boys; this effect was statistically accounted for by covarying of depression and conduct disorder. In the meta-analysis, the composite effect size was OR = 1.22 (95% CI = 1.11-1.34); 22 studies provided effects with medication controlled, yielding a composite effect size of OR = 1.30 (95% CI = 1.12-1.50). Pooled across age the association without covariates was reliable in females (OR = 1.19 [1.01-1.41]) but not males (OR = 1.10 [0.95-1.23]) although males and females did not statistically differ. Pooled across gender, the association was significantly larger in adults (> 18 years) (OR = 1.37 [1.19-1.58]) than in youth (OR = 1.13 [1.00-1.27]), p = .04. Conclusions: ADHD has a small overall association with obesity, but this effect is moderate in adults. The effect is likely to be of no clinical significance in children, possible clinical significance in adolescent girls with comorbid disorders, and of clinical relevance by adulthood. © 2015 Elsevier Ltd.

Nuñez-Forero, L., Moyano-Ariza, L., Gaitán-Duarte, H., Ángel-Müller, E., Ruiz-Parra, A., González, P., et al. (2015). Diagnostic accuracy of rapid tests for sexually transmitted infections in symptomatic women. *Sexually Transmitted Infections,*

Objective To determine the diagnostic accuracy of tests developed for use at the point of care for Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG) and syphilis in women having symptoms of lower urinary tract infection. Methods Cross-sectional study involving sexually active 14-49-year-old women with lower urinary tract infection symptoms consulting during 2010 at a private health clinic and at two public hospitals in Bogotá, Colombia. Pregnant women, those with a previous hysterectomy or those who received antibiotics during the previous 7 days were excluded. Sequential sampling was used; sample size: 1500 women. The ACON NG and CT duo test combo and the ACON individual test plates for NG and separately for CT were used. The

QuickVue Chlamydia rapid test (RT) was also used. All of them were compared with nucleic acid amplification methods. The SD Bioline 3.0 and ACON test for syphilis were evaluated and compared with serological tests. Sensitivity and specificity were estimated. Results CT RTs had a sensitivity that ranged between 22.7% and 37.7% and specificity between 99.3% and 100%. Sensitivity for NG with ACON Duo was 12.5% and specificity 99.8%. Tests for syphilis had a sensitivity of 91.6-100% and a specificity of 99.7-97.8%. Conclusions The RTs studied are not useful for screening for NG at the point of care. In case of CT a recommendation about their use in routine care should be supported by a cost-effectiveness analysis. In screening populations at high risk of sexually transmitted infections or pregnant women, the RTs for syphilis should be used.

O'Glasser, A. Y., & Milas, K. M. (2016). Horner's, heterochromia, and harlequins. *Journal of General Internal Medicine, 31*(1), 137.

Obara, Y., Nagasawa, R., Nemoto, W., Pellegrino, M. J., Takahashi, M., Habecker, B. A., et al. (2016). ERK5 induces ankrd1 for catecholamine biosynthesis and homeostasis in adrenal medullary cells. *Cellular Signalling, 28*(3), 177-189.

Extracellular signal-regulated kinases (ERKs) play important roles in proliferation, differentiation and gene expression. In our previous study, we demonstrated that both ERK5 and ERK1/2 were responsible for neurite outgrowth and tyrosine hydroxylase (TH) expression in rat pheochromocytoma cells (PC12) (J Biol Chem 284, 23,564-23,573, 2009). However, the functional differences between ERK5 and ERK1/2 signaling in neural differentiation remain unclear. In the present study, we show that ERK5, but not ERK1/2 regulates TH levels in rat sympathetic neurons. Furthermore, microarray analysis performed in PC12 cells using ERK5 and ERK1/2-specific inhibitors, identified ankyrin repeat domain 1 (ankrd1) as an ERK5-dependent and ERK1/2-independent gene. Here, we report a novel role of the ERK5/ankrd1 signaling in regulating TH levels and catecholamine biosynthesis. Ankrd1 mRNA was induced by nerve growth factor in time- and concentration-dependent manners. TH levels were reduced by ankrd1 knockdown with no changes in the mRNA levels, suggesting that ankrd1 was involved in stabilization of TH protein. Interestingly, ubiquitination of TH was enhanced and catecholamine

biosynthesis was reduced by ankrd1 knockdown. Finally, we examined the relationship of ERK5 to TH levels in human adrenal pheochromocytomas. Whereas TH levels were correlated with ERK5 levels in normal adrenal medullas, ERK5 was down-regulated and TH was up-regulated in pheochromocytomas, indicating that TH levels are regulated by alternative mechanisms in tumors. Taken together, ERK5 signaling is required for catecholamine biosynthesis during neural differentiation, in part to induce ankrd1, and to maintain appropriate TH levels. This pathway is disrupted in pathological conditions.

O'Glasser, A. Y., & Kent, C. M. (2015). Misdirected by a mass: Syphilis. *The American Journal of Medicine,*

Olivas, A., Gardner, R. T., Wang, L., Ripplinger, C. M., Woodward, W. R., & Habecker, B. A. (2016). Myocardial infarction causes transient cholinergic transdifferentiation of cardiac sympathetic nerves via gp130. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 36*(2), 479-488.

Sympathetic and parasympathetic control of the heart is a classic example of norepinephrine (NE) and acetylcholine (ACh) triggering opposing actions. Sympathetic NE increases heart rate and contractility through activation of beta receptors, whereas parasympathetic ACh slows the heart through muscarinic receptors. Sympathetic neurons can undergo a developmental transition from production of NE to ACh and we provide evidence that mouse cardiac sympathetic nerves transiently produce ACh after myocardial infarction (MI). ACh levels increased in viable heart tissue 10-14 d after MI, returning to control levels at 21 d, whereas NE levels were stable. At the same time, the genes required for ACh synthesis increased in stellate ganglia, which contain most of the sympathetic neurons projecting to the heart. Immunohistochemistry 14 d after MI revealed choline acetyltransferase (ChAT) in stellate sympathetic neurons and vesicular ACh transporter immunoreactivity in tyrosine hydroxylase-positive cardiac sympathetic fibers. Finally, selective deletion of the ChAT gene from adult sympathetic neurons prevented the infarction-induced increase in cardiac ACh. Deletion of the gp130 cytokine receptor from sympathetic neurons prevented the induction of cholinergic genes after MI, suggesting that inflammatory cytokines induce the transient acquisition of a cholinergic phenotype in cardiac sympathetic neurons. Ex

vivo experiments examining the effect of NE and ACh on rabbit cardiac action potential duration revealed that ACh blunted both the NE-stimulated decrease in cardiac action potential duration and increase in myocyte calcium transients. This raises the possibility that sympathetic co-release of ACh and NE may impair adaptation to high heart rates and increase arrhythmia susceptibility. SIGNIFICANCE STATEMENT: Sympathetic neurons normally make norepinephrine (NE), which increases heart rate and the contractility of cardiac myocytes. We found that, after myocardial infarction, the sympathetic neurons innervating the heart begin to make acetylcholine (ACh), which slows heart rate and decreases contractility. Several lines of evidence confirmed that the source of ACh was sympathetic nerves rather than parasympathetic nerves that are the normal source of ACh in the heart. Global application of NE with or without ACh to ex vivo hearts showed that ACh partially reversed the NE-stimulated decrease in cardiac action potential duration and increase in myocyte calcium transients. That suggests that sympathetic co-release of ACh and NE may impair adaptation to high heart rates and increase arrhythmia susceptibility.

Palejwala, N. V., Gale, M. J., Clark, R. F., Schlechter, C., Weleber, R. G., & Pennesi, M. E. (2016). Insights into autosomal dominant stargardt-like macular dystrophy through multimodality diagnostic imaging. *Retina, 36*(1), 119-130.

Purpose: Autosomal dominant Stargardt-like macular dystrophy is a rare juvenile macular dystrophy most commonly because of mutations in ELOVL4 and PROM1 genes. In this study, we review a series of cases of Stargardt-like macular dystrophy and use advanced imaging techniques to describe pathophysiologic manifestations. Methods: A retrospective medical record review was performed for five patients from two families with ELOVL4 mutation and one patient with PROM1 mutation including reviewing diagnostic imaging, such as fundus photography, spectral domain optical coherence tomography, fundus autofluorescence, and adaptive optics flood-illuminated photography. Results: All patients had reduced central visual acuity with varying degree of foveal atrophy. In the ELOVL4 group, best-corrected visual acuity ranged from 20/25 to 20/200. Early pathologic changes included thickening of the external limiting membrane and outer nuclear atrophy followed by retinal pigment epithelium loss in later stages. Adaptive optics imaging revealed photoreceptor loss even in early stages with good visual acuity. The PROM1 patient also had similar central vision loss with significant outer nuclear atrophy. In

contrast to ELOVL4 mutation, there was more diffuse and patchy retinal pigment epithelium loss throughout the macula. Conclusion: Both ELOVL4- and PROM1-related maculopathies are characterized by progressive photoreceptor atrophy and central vision loss. Using advanced diagnostic imaging, early disease changes and disease progression can be characterized.

Pazos, M., Yang, H., Gardiner, S. K., Cepurna, W. O., Johnson, E. C., Morrison, J. C., et al. (2016). Expansions of the neurovascular scleral canal and contained optic nerve occur early in the hypertonic saline rat experimental glaucoma model. *Experimental Eye Research, 145*, 173-186. Purpose: To characterize early optic nerve head (ONH) structural change in rat experimental glaucoma (EG). Methods: Unilateral intraocular pressure (IOP) elevation was induced in Brown Norway rats by hypertonic saline injection into the episcleral veins and animals were sacrificed 4 weeks later by perfusion fixation. Optic nerve cross-sections were graded from 1 (normal) to 5 (extensive injury) by 5 masked observers. ONHs with peripapillary retina and sclera were embedded, serial sectioned, 3-D reconstructed, delineated, and quantified. Overall and animal-specific EG versus Control eye ONH parameter differences were assessed globally and regionally by linear mixed effect models with significance criteria adjusted for multiple comparisons. Results: Expansions of the optic nerve and surrounding anterior scleral canal opening achieved statistical significance overall ($p < 0.0022$), and in 7 of 8 EG eyes ($p < 0.005$). In at least 5 EG eyes, significant expansions ($p < 0.005$) in Bruch's membrane opening (BMO) (range 3-10%), the anterior and posterior scleral canal openings (8-21% and 5-21%, respectively), and the optic nerve at the anterior and posterior scleral canal openings (11-30% and 8-41%, respectively) were detected. Optic nerve expansion was greatest within the superior and inferior quadrants. Optic nerve expansion at the posterior scleral canal opening was significantly correlated to optic nerve damage ($R = 0.768$, $p = 0.042$). Conclusion: In the rat ONH, the optic nerve and surrounding BMO and neurovascular scleral canal expand early in their response to chronic experimental IOP elevation. These findings provide phenotypic landmarks and imaging targets for detecting the development of experimental glaucomatous optic neuropathy in the rat eye.

Penney, L. S., Ritenbaugh, C., Elder, C., Schneider, J., Deyo, R. A., & DeBar, L. L. (2016). Primary care physicians, acupuncture and chiropractic clinicians, and chronic pain patients: A qualitative analysis of communication and care coordination patterns. *BMC Complementary and Alternative Medicine, 16*(1), 30-016-1005-4.

BACKGROUND: A variety of people, with multiple perspectives, make up the system comprising chronic musculoskeletal pain (CMP) treatment. While there are frequently problems in communication and coordination of care within conventional health systems, more opportunities for communicative disruptions seem possible when providers use different explanatory models and are not within the same health management system. We sought to describe the communication system surrounding the management of chronic pain from the perspectives of allopathic providers, acupuncture and chiropractor (A/C) providers, and CMP patients. METHODS: We collected qualitative data from CMP patients (n = 90) and primary care physicians (PCPs) (n = 25) in a managed care system, and community acupuncture and chiropractic care providers (n = 14) who received high levels of referrals from the system, in the context of a longitudinal study of CMP patients' experience. RESULTS: Multiple points of divergence and communicative barriers were identified among the main stakeholders in the system. Those that were most frequently mentioned included issues surrounding the referral process (requesting, approving) and lack of consistent information flow back to providers that impairs overall management of patient care. We found that because of these problems, CMP patients were frequently tasked and sometimes overwhelmed with integrating and coordinating their own care, with little help from the system. CONCLUSIONS: Patients, PCPs, and A/C providers desire more communication; thus systems need to be created to facilitate more open communication which could positively benefit patient outcomes.

Pham, A. N., Bubalo, J. S., & Lewis, J. S.,2nd. (2016). Comparison of posaconazole serum concentrations from haematological cancer patients on posaconazole tablet and oral suspension for treatment and prevention of invasive fungal infections. *Mycoses,*

Posaconazole tablet formulation (PTF) was developed to optimise bioavailability. This study compared posaconazole levels between patients on the PTF and oral suspension formulation (OSF). We also examined factors that may impact posaconazole levels. The primary and

secondary objectives were analysed by comparing trough levels and attainment of target level between the formulation groups. For the 86 patients on PTF and 176 on OSF, the mean first levels was 1.32 mug ml-1 (SD = 0.69) and 0.81 mug ml-1 (SD = 0.59), P /=0.7 mug ml-1 than OSF group (OR 7.97 [95 CI; 3.75-16.93], P < 0.0001). Levels from patients on PTF and with presence of acid suppression, GI GVHD, mucositis or diarrhoea were not statistically different from those without these factors. For PTF, no correlation was found between patient's weight (kg) and levels (R2 = 0.0536, P = 0.035). The incidences of elevation in ALT/AST or Tbili were similar between the formulation groups. In conclusion, PTF should be considered the preferred formulation because it demonstrated better absorption than the OSF. Patients on PTF for prophylaxis are more likely to attain target level and may not routinely require therapeutic drug monitoring during prophylaxis.

Phan, L., Grimm, C., & Rugonyi, S. (2015). In Elendt M., et al(Eds.), *Visualization techniques for the developing chicken heart* Springer Verlag.

We present a geometric surface parameterization algorithm and several visualization techniques adapted to the problem of understanding the 4D peristaltic-like motion of the outflow tract (OFT) in an embryonic chick heart. We illustrated the techniques using data from hearts under normal conditions (four embryos), and hearts in which blood flow conditions are altered through OFT banding (four embryos). The overall goal is to create quantitative measures of the temporal heartshape change both within a single subject and between multiple subjects. These measures will help elucidate how altering hemodynamic conditions changes the shape and motion of the OFT walls, which in turn influence the stresses and strains on the developing heart, causing it to develop differently. We take advantage of the tubular shape and periodic motion of the OFT to produce successively lower dimensional visualizations and quantifications of the cardiac motion.

Pharaon, K. S., & Trunkey, D. D. (2015). Abdominal abscess. (pp. 366-369) Cambridge University Press.

Intra-abdominal infections generally occur after entry of enteric organisms into the peritoneal cavity. An abscess is the body’s way of attempting to contain an infection. Intraperitoneal and

retroperitoneal abscesses can develop as a result of appendicitis, diverticulitis, necrotizing enterocolitis, pancreatitis, pelvic inflammatory disease, tubo-ovarian infection, surgery, or trauma. Given the vast number of microbes in our alimentary tract, any penetration of the wall of the gastrointestinal (GI) tract as a result of a vascular, traumatic, or iatrogenic event introduces these microbes into the abdomen. The concentration of microorganisms increases with distal progression down the GI tract. The morbidity of an intra-abdominal infection is 40%. The mortality is 20% in immunocompetent patients, and can be as high as 70% in the immunocompromised. This chapter explains types of peritonitis, locations of abscesses, diagnosis, treatment, common organisms associated with community-acquired and healthcare-associated infections, and suggested use of antimicrobials. Abdominal abscess often follows or complicates peritonitis (see Chapter 57, Peritonitis). Primary peritonitis is an infection of the peritoneal cavity without an underlying violation of the intestinal wall; the most common cause of primary peritonitis is spontaneous bacterial peritonitis (SBP). The etiology of SBP is thought to be translocation of bacteria through the intestinal wall and into the abdomen. Clinical features of SBP may be subtle or absent, but usually SBP causes abdominal pain from infected ascites. The mainstay of treatment of primary peritonitis is antibiotics. Secondary peritonitis results from perforation of hollow viscera with spillage of intestinal contents, often from appendicitis, diverticulitis, or ulceration. The patient may initially present with severe abdominal pain, tenderness, rigid abdomen, or shock. The peritonitis can be focal or diffuse. If the spillage is small, the patient may not initially seek medical attention. Over the course of a few days the body will attempt to contain it, and an abscess may develop. If the abscess is less than 3 cm, the patient may only need antibiotics. An abscess 3 cm or greater usually needs drainage, and the percutaneous approach is preferred. Some abdominal abscesses progress to severe sepsis and shock, particularly when left untreated. Immunocompromised patients may have perforation with gross contamination of their abdomen, yet be relatively asymptomatic, making diagnosis more challenging. Tertiary peritonitis is a persistent or recurrent infection following treatment of primary or secondary peritonitis and is often found in patients with pre-existing comorbidities or who are immunocompromised.

Phillips, T. J., Eastwood, E. C., & Harkness, J. H. (2014). Drug abuse: Amphetamines. (pp. 330-349) Cambridge University Press.

Amphetamine and amphetamine analogues, such as methamphetamine and 3, 4-methylenedioxymethamphetamine (MDMA), have been used for many reasons. Amphetamine has well-known stimulant properties and was once commonly prescribed for treatment of depression and obesity (Anglin et al., 2000). Amphetamine-like drugs and psychostimulants such as methylphenidate and modainil are currently sometimes prescribed for treatment of attention-deicit hyperactivity disorder (ADHD) and narcolepsy, and may be "self-prescribed" as cognitive enhancers (Fredriksen et al., 2013; Hirai and Nishino, 2011; Steiner and Van Waes, 2013). However, amphetamines have profound abuse potential and a high risk for neurotoxicity with chronic use and dependency. More signiicant problems with addiction tomethamphetamine are currently seen and the clinical pharmacology has been nicely reviewed (Cruickshank and Dyer, 2009). However, a recent paper compared the efects of intranasal d-amphetamine and methamphetamine on mood, performance, and physiological efects in humans and concluded that the drugs have similar dose-related proiles of efects and may therefore have equivalent abuse potential (Kirkpatrick et al., 2012a). © Cambridge University Press 2014.

Picelli, A., Herman, T., Paul, S. S., & King, L. A. (2015). Rehabilitation procedures in the management of parkinson's disease. *Parkinson's Disease, 2015*, 824056.

Pillay, S., Meyer, N. L., Puschnik, A. S., Davulcu, O., Diep, J., Ishikawa, Y., et al. (2016). An essential receptor for adeno-associated virus infection. *Nature,*

Adeno-associated virus (AAV) vectors are currently the leading candidates for virus-based gene therapies because of their broad tissue tropism, non-pathogenic nature and low immunogenicity. They have been successfully used in clinical trials to treat hereditary diseases such as haemophilia B (ref. 2), and have been approved for treatment of lipoprotein lipase deficiency in Europe. Considerable efforts have been made to engineer AAV variants with novel and biomedically valuable cell tropisms to allow efficacious systemic administration, yet basic aspects of AAV cellular entry are still poorly understood. In particular, the protein receptor(s) required for AAV entry after cell attachment remains unknown. Here we use an unbiased genetic screen to

identify proteins essential for AAV serotype 2 (AAV2) infection in a haploid human cell line. The most significantly enriched gene of the screen encodes a previously uncharacterized type I transmembrane protein, KIAA0319L (denoted hereafter as AAV receptor (AAVR)). We characterize AAVR as a protein capable of rapid endocytosis from the plasma membrane and trafficking to the trans-Golgi network. We show that AAVR directly binds to AAV2 particles, and that anti-AAVR antibodies efficiently block AAV2 infection. Moreover, genetic ablation of AAVR renders a wide range of mammalian cell types highly resistant to AAV2 infection. Notably, AAVR serves as a critical host factor for all tested AAV serotypes. The importance of AAVR for in vivo gene delivery is further highlighted by the robust resistance of Aavr-/- (also known as Au040320-/- and Kiaa0319l-/-) mice to AAV infection. Collectively, our data indicate that AAVR is a universal receptor involved in AAV infection.

Prakasam, S., Stein, K., Lee, M. K., Rampa, S., Nalliah, R., Allareddy, V., et al. (2016). Prevalence and predictors of complications following facial reconstruction procedures. *International Journal of Oral and Maxillofacial Surgery,*

Facial reconstruction procedures are immensely challenging and are done for a multitude of reasons. The purpose of this report is to provide nationally representative estimates of different types of facial reconstructive procedures and to examine prevalence and predictors of a wide range of complications associated with these procedures in the USA. The Nationwide Inpatient Sample, the largest inpatient dataset for the USA, was used. Data for the years 2004-2010 related to facial reconstruction procedures were identified through ICD-9-CM procedure codes. Associated complications were identified using secondary diagnosis field codes. Multivariable logistic regression models were used to examine the association between patient/hospital-level factors and the occurrence of complications. A total 26,374 facial reconstruction procedures were performed. About 20% of all patients who had facial reconstruction procedures developed a complication. Frequently occurring complications included postoperative pneumonia (4.9% of hospitalizations), hemorrhage (3.9%), other infections (3.6%), non-healing wounds (3.5%), and iatrogenically induced complications (3.2%). Significant factors found to be consistently associated with different types of complications included age, co-morbid burden, sex, and type of admission. The reported results are generalizable within limitations and can be used by health

care providers to tailor quality improvement initiatives to minimize or better treat complications in the high-risk cohorts.

Prasad, V. (2016). Reply to dr. leon: True but unrelated. *Journal of Clinical Epidemiology,*

Prasad, V., & Berger, V. W. (2016). In reply-is there a need for "bias police" in industry-sponsored research? *Mayo Clinic Proceedings, 91*(1), 121.

Prasad, V., Lenzer, J., & Newman, D. H. (2016). Why cancer screening has never been shown to "save lives"-and what we can do about it. *BMJ (Clinical Research Ed.), 352*, h6080.

Pulido, J. S., Flaxel, C. J., Adelman, R. A., Hyman, L., Folk, J. C., & Olsen, T. W. (2016). Retinal vein occlusions. *Ophthalmology, 123*(1), P182-P208.

Puljic, A., & Caughey, A. B. (2015). Reply. *American Journal of Obstetrics and Gynecology,*

Puljic, A., Salati, J., Doss, A., & Caughey, A. B. (2016). Outcomes of pregnancies complicated by liver cirrhosis, portal hypertension, or esophageal varices. *Journal of Maternal-Fetal and Neonatal Medicine, 29*(3), 506-509.

Objective: To evaluate pregnancy outcomes in women with liver cirrhosis, portal hypertension, or esophageal varices.Study design: We analyzed a retrospective cohort of 2 284 218 pregnancies in 2005-2009 recorded in the California Birth Registry database. Utilizing ICD-9 codes we analyzed the following outcomes for liver cirrhosis, portal hypertension, or esophageal varices in pregnancy: preeclampsia (PET), preterm delivery (PTD; <37 weeks), cesarean section, low birth weight (LBW; <2500 g), small for gestational age (SGA; <10th percentile), neonatal death (NND), and postpartum hemorrhage (PPH).Results: Cirrhosis in pregnancy conferred an increased risk of PET, PTD, CS in multiparous women, LBW, and NND. Portal hypertension in pregnancy was associated with PTD, LBW, NND, and PPH. Non-bleeding esophageal varices in pregnancy were not associated with the outcomes assessed in a statistically significant manner. One case of bleeding esophageal varices was observed, resulting in PTD with a LBW infant. There were three cases of concomitant portal hypertension or concomitant esophageal varices with cirrhosis in pregnancy.Conclusion: Pregnancy in women with concomitant liver cirrhosis, portal hypertension,

or esophageal varices can be successful. However, pregnancy outcomes are worse and may warrant closer antenatal monitoring and patient counseling. Cirrhosis in pregnancy with concomitant portal hypertension or esophageal varices is rare. © 2015 Informa UK Ltd.

Raber, J., Allen, A. R., Weber, S., Chakraborti, A., Sharma, S., & Fike, J. R. (2016). Effect of behavioral testing on spine density of basal dendrites in the CA1 region of the hippocampus modulated by fe irradiation. *Behavioural Brain Research, 302*, 263-268.

A unique feature of the space radiation environment is the presence of high-energy charged particles, including 56Fe ions, which can present a significant hazard to space flight crews during and following a mission. 56Fe irradiation-induced cognitive changes often involve alterations in hippocampal function. These alterations might involve changes in spine morphology and density. In addition to irradiation, performing a cognitive task can also affect spine morphology. Therefore, it is often hard to determine whether changes in spine morphology and density are due to an environmental challenge or group differences in performance on cognitive tests. In this study, we tested the hypothesis that the ability of exploratory behavior to increase specific measures of hippocampal spine morphology and density is affected by 56Fe irradiation. In sham-irradiated mice, exploratory behavior increased basal spine density in the CA1 region of the hippocampus and the enclosed blade of the dentate gyrus. These effects were not seen in irradiated mice. In addition, following exploratory behavior, there was a trend toward a decrease in the percent stubby spines on apical dendrites in the CA3 region of the hippocampus in 56Fe-irradiated, but not sham-irradiated, mice. Other hippocampal regions and spine measures affected by 56Fe irradiation showed comparable radiation effects in behaviorally naive and cognitively tested mice. Thus, the ability of exploratory behavior to alter spine density and morphology in specific hippocampal regions is affected by 56Fe irradiation.

Rajhbeharrysingh, U., El Youssef, J., Leon, E., Lasarev, M. R., Klein, R., Vanek, C., et al. (2016). Expanding the net: The re-evaluation of the multidimensional nomogram calculating the upper limit of normal PTH (maxPTH) in the setting of secondary hyperparathyroidism and the development of the MultIdimensional predictive hyperparaTHyroid model (mi-PTH). *Surgery (United States), 159*(1), 226-239.

Background The multidimensional nomogram calculating the upper limit of normal PTH (maxPTH) model identifies a personalized upper limit of normal parathyroid hormone (PTH) and successfully predicts classical primary hyperparathyroidism (PHP). We aimed to assess whether maxPTH can distinguish normocalcemic PHP (NCPHP) from secondary hyperparathyroidism (SHP), including subjects who underwent bariatric surgery (BrS). Methods A total of 172 subjects with 359 complete datasets of serum calcium (Ca), 25-OH vitamin D, and intact PTH from Oregon were analyzed: 123 subjects (212 datasets) with PHP and 47 (143) with SHP, including 28 (100) with previous BrS. An improved prediction model, MultIdimensional evaluation for Primary hyperparaTHyroidism (Mi-PTH), was created with the same variables as maxPTH by the use of a combined cohort (995 subjects) including participants from previous studies. Results In the Oregon cohort, maxPTH's sensitivity was 100% for classical PHP and 89% for NCPHP, but only 50% for normohormonal PHP (NHPHP) and 40% specific for SHP. In comparison, although sensitivity for NCPHP was similar (89%), Mi-PTH vastly improved SHP specificity (85%). In the combined cohort, Mi-PTH had better sensitivity of 98.5% (vs 95%) and specificity 97% (vs 85%). Conclusion MaxPTH was sensitive in detecting PHP; however, there was low specificity for SHP, especially in patients who underwent BrS. The creation of Mi-PTH provided improved performance measures but requires further prospective evaluation. © 2016 Elsevier Inc.

Reichardt, P., Demetri, G. D., Gelderblom, H., Rutkowski, P., Im, S. -., Gupta, S., et al. (2016). Correlation of KIT and PDGFRA mutational status with clinical benefit in patients with gastrointestinal stromal tumor treated with sunitinib in a worldwide treatment-use trial. *BMC Cancer, 16*(1)

Background: Several small studies indicated that the genotype of KIT or platelet-derived growth factor receptor-aα (PDGFRA) contributes in part to the level of clinical effectiveness of sunitinib in gastrointestinal stromal tumor (GIST) patients. This study aimed to correlate KIT and PDGFRA mutational status with clinical outcome metrics (progression-free survival [PFS], overall survival [OS], objective response rate [ORR]) in a larger international patient population. Methods: This is a non-interventional, retrospective analysis in patients with imatinib-resistant or intolerant GIST who were treated in a worldwide, open-label treatment-use study (Study 1036; NCT00094029) in which sunitinib was administered at a starting dose of 50 mg/day on a 4-week-on, 2-week-off

schedule. Molecular status was obtained in local laboratories with tumor samples obtained either pre-imatinib, post-imatinib/pre-sunitinib, or post-sunitinib treatment, and all available data were used in the analyses regardless of collection time. The primary analysis compared PFS in patients with primary KIT exon 11 versus exon 9 mutations (using a 2-sided log-rank test) and secondary analyses compared OS (using the same test) and ORR (using a 2-sided Pearson χ2 test) in the same molecular subgroups. Results: Of the 1124 sunitinib-treated patients in the treatment-use study, 230 (20 %) were included in this analysis, and baseline characteristics were similar between the two study populations. Median PFS was 7.1 months. A significantly better PFS was observed in patients with a primary mutation in KIT exon 9 (n = 42) compared to those with a primary mutation in exon 11 (n = 143; hazard ratio = 0.59; 95 % confidence interval, 0.39-0.89; P = 0.011), with median PFS times of 12.3 and 7.0 months, respectively. Similarly, longer OS and higher ORR were observed in patients with a primary KIT mutation in exon 9 versus exon 11. The data available were limited to investigate the effects of additional KIT or PDGFRA mutations on the efficacy of sunitinib treatment. Conclusions: This large retrospective analysis confirms the prognostic significance of KIT mutation status in patients with GIST. This analysis also confirms the effectiveness of sunitinib as a post-imatinib therapy, regardless of mutational status. © 2016 Reichardt et al.

Reinier, K., Narayanan, K., Uy-Evanado, A., Teodorescu, C., Chugh, H., Mack, W. J., et al. (2015). Electrocardiographic markers and left ventricular ejection fraction have cumulative effects on risk of sudden cardiac death. *JACC: Clinical Electrophysiology, 1*(6), 542-550.

Objectives This study assessed potential improvement in predicting risk of sudden cardiac death (SCD) by adding selected risk markers from the 12-lead electrocardiogram (ECG) to the measurement of left ventricular ejection fraction (LVEF). Background Novel strategies to improve risk stratification for SCD are needed. Given the modest odds associated with most individual risk markers, combining multiple markers may be a useful approach. Methods From the ongoing Oregon Sudden Unexpected Death Study, SCD cases with pre-event LVEF data available were compared with those of matched control subjects with coronary artery disease. Resting heart rate, QRS duration (QRSD), and JTc intervals were measured from archived ECGs prior to and unrelated to the SCD event. Independent odds of SCD for individual and combined ECG markers

were calculated. Results SCD cases (n = 317; 67.9 ± 12.9 years of age) were more likely than controls (n = 317; 67.9 ± 12.8 years of age) to have LVEF ≤35% (26% vs. 11%, respectively). Mean heart rate, QRSD, and JTc were significantly higher in cases (all p < 0.0001). In adjusted analyses, higher heart rate (odds ratio [OR]: 2.6 [95% confidence interval [CI]: 1.8 to 3.7]), QRSD (OR: 1.5 [95% CI: 1.0 to 2.5]), and JTc (OR: 2.3 [95% CI: 1.6 to 3.4]) were independently associated with SCD. When ECG markers were combined, SCD odds progressively increased with 1 (OR: 3.4 [95% CI: 2.1 to 5.4]) and ≥2 elevated markers (OR: 6.3 [95% CI: 3.3 to 12.1]). Addition of ECG markers to an adjusted model with LVEF improved discrimination (C statistic improved from 0.642 to 0.724) and net reclassification (by 22.7%; p < 0.0001). Conclusions Combining selected 12-lead ECG markers with LVEF improves SCD risk prediction and warrants further investigation in prospective studies. © 2015 American College of Cardiology Foundation.

Ren, T., He, W., & Barr-Gillespie, P. G. (2016). Reverse transduction measured in the living cochlea by low-coherence heterodyne interferometry. *Nature Communications, 7*, 10282.

It is generally believed that the remarkable sensitivity and frequency selectivity of mammalian hearing depend on outer hair cell-generated force, which amplifies sound-induced vibrations inside the cochlea. This 'reverse transduction' force production has never been demonstrated experimentally, however, in the living ear. Here by directly measuring microstructure vibrations inside the cochlear partition using a custom-built interferometer, we demonstrate that electrical stimulation can evoke both fast broadband and slow sharply tuned responses of the reticular lamina, but only a slow tuned response of the basilar membrane. Our results indicate that outer hair cells can generate sufficient force to drive the reticular lamina over all audible frequencies in living cochleae. Contrary to expectations, the cellular force causes a travelling wave rather than an immediate local vibration of the basilar membrane; this travelling wave vibrates in phase with the reticular lamina at the best frequency, and results in maximal vibration at the apical ends of outer hair cells.

Riccelli, L. P., Cameron, M., Burke, A. G., & Mazumder, R. (2014). Spinal cord trauma. (pp. 249-259) Cambridge University Press.

This chapter discusses the clinical and radiologic examination and findings for patients with known or suspected acute spinal cord trauma. It does not cover injury to other structures of the spine, including the discs, ligaments, and vertebrae, except as these relate to acute spinal cord trauma. The average estimated incidence of traumatic spinal cord injury (SCI) in the United States is 40 per million, which is higher than in the rest of the world [1]. In Western Europe, the median incidence of traumatic SCI is 16 per million, with reports ranging from 9.2 per million in Denmark to 33.6 per million in Greece [2]. In the United States, motor-vehicle crashes (MVCs) are the most common cause of SCI overall although, in people over 60, falls are the most common cause. In developed countries, the proportion of traumatic SCI due to MVCs tends to be stable or decreasing, likely due to safer cars and better infrastructure. In developing countries, the proportion of SCI caused by MVCs is increasing, likely because motor-vehicle use is increasing without standardized vehicle safety equipment or infrastructure. Injuries from falls in the elderly are also increasing in developed countries as the proportion of the population surviving to old age increases. In addition, SCI due to violence is more common in South Africa, the Middle East, Brazil, and the USA than in the rest of the world [2]. The mechanism and level of SCI also vary by age and gender. Rates are lowest in young children and highest in persons in their late teens or early twenties, with a possible secondary peak among the elderly [1]. SCI is three to four times more common in males than in females. In children younger than 8 years of age, SCI is more commonly due to MVCs, more commonly involves the upper cervical spine, and more commonly involves injury to the ligaments or spinal cord without necessarily involving the bones. In contrast, in children older than 8 years of age, SCI is most commonly sports-related, peaking at 13–15 years of age, is more common in males, and more often involves the lower cervical spine [3].

Rice, T. W., Ishwaran, H., Hofstetter, W. L., Schipper, P. H., Kesler, K. A., Law, S., et al. (2016). Esophageal cancer: Associations with (pN+) lymph node metastases. *Annals of Surgery,* OBJECTIVES:: To identify the associations of lymph node metastases (pN+), number of positive nodes, and pN subclassification with cancer, treatment, patient, geographic, and institutional variables, and to recommend extent of lymphadenectomy needed to accurately detect pN+ for esophageal cancer. SUMMARY BACKGROUND DATA:: Limited data and traditional analytic

techniques have precluded identifying intricate associations of pN+ with other cancer, treatment, and patient characteristics. METHODS:: Data on 5806 esophagectomy patients from the Worldwide Esophageal Cancer Collaboration were analyzed by Random Forest machine learning techniques. RESULTS:: pN+, number of positive nodes, and pN subclassification were associated with increasing depth of cancer invasion (pT), increasing cancer length, decreasing cancer differentiation (G), and more regional lymph nodes resected. Lymphadenectomy necessary to accurately detect pN+ is 60 for shorter, well-differentiated cancers (<2.5?cm) and 20 for longer, poorly differentiated ones. CONCLUSIONS:: In esophageal cancer, pN+, increasing number of positive nodes, and increasing pN classification are associated with deeper invading, longer, and poorly differentiated cancers. Consequently, if the goal of lymphadenectomy is to accurately define pN+ status of such cancers, few nodes need to be removed. Conversely, superficial, shorter, and well-differentiated cancers require a more extensive lymphadenectomy to accurately define pN+ status.

Rich, P., Gooderham, M., Bachelez, H., Goncalves, J., Day, R. M., Chen, R., et al. (2016). Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *Journal of the American Academy of Dermatology, 74*(1), 134-142.

Background In the phase III double-blind Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) 1 and 2, apremilast, an oral phosphodiesterase 4 inhibitor, demonstrated efficacy in moderate to severe psoriasis. Objective We sought to evaluate efficacy of apremilast in nail/scalp psoriasis in ESTEEM 1 and 2. Methods A total of 1255 patients were randomized (2:1) to apremilast 30 mg twice daily or placebo. At week 16, placebo patients switched to apremilast through week 32, followed by a randomized withdrawal phase to week 52. A priori efficacy analyses included patients with nail (target nail Nail Psoriasis Severity Index score ≥1) and moderate to very severe scalp (Scalp Physician Global Assessment score ≥3) psoriasis at baseline. Results At baseline, 66.1% and 64.7% of patients had nail psoriasis; 66.7% and 65.5% had moderate to very severe scalp psoriasis in ESTEEM 1 and 2. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index score versus placebo; mean percent change: -22.5% versus +6.5% (ESTEEM 1; P < .0001) and -29.0% versus -7.1%

(ESTEEM 2; P = .0052). At week 16, apremilast produced greater NAPSI-50 response (50% reduction from baseline in target nail Nail Psoriasis Severity Index score) versus placebo (both studies P < .0001) and ScPGA response (Scalp Physician Global Assessment score 0 or 1) versus placebo (both studies P < .0001). Improvements were generally maintained over 52 weeks in patients with Psoriasis Area and Severity Index response at week 32. Limitations Baseline randomization was not stratified for nail/scalp psoriasis. Conclusion Apremilast reduces the severity of nail/scalp psoriasis.

Rigg, R. A., Healy, L. D., Nowak, M. S., Mallet, J., Thierheimer, M. L., Pang, J., et al. (2016). Heat shock protein 70 (Hsp70) regulates platelet integrin activation, granule secretion and aggregation. *American Journal of Physiology.Cell Physiology,* , ajpcell.00362.2015.

Molecular chaperones that support protein quality control, including heat shock protein 70 (Hsp70), participate in diverse aspects of cellular and physiological function. Recent studies have reported roles for specific chaperone activities in blood platelets in maintaining hemostasis; however, the functions of Hsp70 in platelet physiology remain uninvestigated. Here we characterize roles for Hsp70 activity in platelet activation and function. In vitro biochemical, microscopy, flow cytometry and aggregometry assays of platelet function as well as ex vivo analyses of platelet aggregate formation in whole blood under shear were carried out under Hsp70-inhibited conditions. Inhibition of platelet Hsp70 blocked platelet aggregation and granule secretion in response to collagen-related peptide (CRP), which engages the ITAM-bearing collagen receptor GPVI/FcRgamma complex. Hsp70 inhibition also reduced platelet alphaIIbbeta3 activation downstream of GPVI, as Hsp70-inhibited platelets showed reduced PAC-1 and fibrinogen binding. Ex vivo, pharmacological inhibition of Hsp70 in whole human blood prevented the formation of platelet aggregates on collagen under shear. Biochemical studies supported a role for Hsp70 in maintaining the assembly of the linker for activation of T cells (LAT) signalosome, which couples GPVI-initiated signaling to integrin activation, secretion and platelet function. Together, our results suggest that Hsp70 regulates platelet activation and function by supporting LAT-associated signaling events downstream of platelet GPVI engagement, suggesting a role for Hsp70 in the intracellular organization of signaling systems that mediate platelet

secretion, "inside-out" activation of platelet integrin alphaIIbbeta3, platelet-platelet aggregation, and ultimately hemostatic plug and thrombus formation.

Riley, A. R., Freeman, K. A., & Marshall, S. (2016). Dissemination of evidence-based behavioral advice via video in pediatric primary care: An acceptance and utilization study. *Clinical Pediatrics, 55*(2), 122-128.

Background. Research suggests that multimedia-based interventions possess advantages for disseminating safe and effective methods of behavior management to parents in pediatric primary care; however, little is known about their utilization in real-life settings. In order to maximize the impact of multimedia resources, more knowledge regarding dissemination and implementation is needed. Objective. To examine provider and parental perception and utilization of videos designed to communicate evidence-based parenting strategies for disruptive behavior. Videos were available in clinic and online. Results. Both provider and parent perceptions of the videos were largely positive. However, of 240 parents surveyed, only 33% were aware of the availability of videos subsequent to a well-child visit. Parents were unlikely to view the videos if they did not do so as part of their child's health care visit. Conclusion. Multimedia interventions for behavior management are likely to be well received, but systematic methods of implementation are needed. Further study of dissemination of multimedia interventions is merited. © SAGE Publications.

Rivera-Grana, E., Lin, P., Suhler, E. B., & Rosenbaum, J. T. (2015). Methotrexate as a corticosteroid-sparing agent for thyroid eye disease. *Journal of Clinical & Experimental Ophthalmology, 6*(2), 422. Epub 2015 Apr 27.

OBJECTIVE: Thyroid eye disease (TED) is generally treated with oral corticosteroid therapy. A steroid sparing drug could be a useful adjunct. We reviewed our experience with methotrexate as a corticosteroid sparing agent to treat TED. METHODS: Retrospective chart review from two eye inflammation clinics. Patients with TED who were unable to discontinue prednisone therapy without disease recurrence were included. RESULTS: 14 patients who were receiving an average of 32 mg/day of prednisone were treated with methotrexate, usually 15 mg/week orally or 20 mg/week subcutaneously. Five patients discontinued therapy for a lack of benefit or intolerance.

Of the 9 patients who remained on methotrexate, all were able to discontinue prednisone completely after an average duration of 7.5 months. Improved visual acuity by at least two lines on the Snellen chart was achieved by 7 of 12 patients with reduced acuity and partial improvement in ocular motility was achieved in 5 of 14 patients. CONCLUSIONS: Methotrexate provided an effective steroid sparing effect in a subset of patients with TED.

Rodriguez, S. A., Impey, S. D., Pelz, C., Enestvedt, B., Bakis, G., Owens, M., et al. (2016). RNA sequencing distinguishes benign from malignant pancreatic lesions sampled by EUS-guided FNA. *Gastrointestinal Endoscopy,*

BACKGROUND AND AIMS: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is the primary method used to obtain pancreatic tissue for preoperative diagnosis. Accumulating evidence suggests diagnostic and prognostic information may be obtained by gene expression profiling of these biopsies. RNA sequencing is a newer method of gene expression profiling. There is scant published data on the use of this method on pancreas tissue obtained via EUS-FNA. The aim of this study was to determine whether RNA sequencing of EUS-FNA biopsies of undiagnosed pancreatic masses can reliably discriminate between benign and malignant tissue. METHODS: Prospective study of consenting adults presenting to two tertiary care hospitals for EUS of suspected pancreatic mass. Tissue was submitted for RNA sequencing. The results were compared with cytologic diagnosis, surgical pathology diagnosis, or benign clinical follow-up of at least 1 year. RESULTS: Forty-eight patients with solid pancreatic mass lesions were enrolled. Nine samples were excluded due to inadequate RNA and 3 were excluded due to final pathologic diagnosis of neuroendocrine tumor. Data from the first 13 patients was used to construct a linear classifier and this was tested on the final 23 patients (n = 15 malignant and n=8 benign lesions). RNA sequencing of EUS-FNA biopsies distinguishes ductal adenocarcinoma from benign pancreatic solid masses with a sensitivity of 0.87 (0.58-0.98) and specificity of 0.75 (0.35-0.96). CONCLUSIONS: This proof of principle study suggests RNA sequencing of EUS-FNA samples can reliably detect adenocarcinoma and may provide a new method to evaluate more diagnostically challenging pancreatic lesions.

Rosenbaum, J. T., Lin, P., & Asquith, M. (2016). The microbiome, HLA, and the pathogenesis of uveitis. *Japanese Journal of Ophthalmology, 60*(1), 1-6.

An understanding of the microbiome is emerging as an exciting and novel way to elucidate the regulation of the immune system. Since the immune system plays a major role in the pathogenesis of many diseases including most forms of uveitis, it is critical to clarify the relationship between our immune system and the commensal bacteria that coexist in every human being. © 2015, Japanese Ophthalmological Society.

Rosen-Reynoso, M., Porche, M. V., Kwan, N., Bethell, C., Thomas, V., Robertson, J., et al. (2016). Disparities in access to easy-to-use services for children with special health care needs. *Maternal and Child Health Journal,*

Objectives Families, clinicians and policymakers desire improved delivery of health and related services for children with special health care needs (CSHCN). We analyzed factors associated with ease of use in obtaining such services. We also explored what were specific difficulties or delays in receiving services. By examining data from the National Survey of Children with Special Health Care Needs (NS-CSHCN 2009-2010) and using the revised criteria for "ease of use," we were able to assess the percentage of parents who reported that their experiences seeking services for their children met those criteria. Methods We performed Chi square tests to examine associations between the independent variables and their relationship to the difficulties or delays assessed in the survey; including: eligibility, availability of services, waiting lists, cost, and access to information. We used logistic regression to determine the association of meeting the "ease of use" criteria with socio-demographic, complexity of need, and access variables. Results Overall, a third of families of CSHCN (35.3 %) encounter difficulties, delays, or frustrations in obtaining health and related services. The lack of access to health and community services in this study fell most heavily on children from racial/ethnic minority backgrounds, those in poverty, and those with complex emotional/behavioral or developmental needs and functional limitations. Conclusions for Practice CSHCN require services from a broad array of providers across multiple systems. Unfortunately, there are certain difficulties that hamper the accessibility of these systems. These findings underscore the need for both practice-level response and systems-level reform to ensure equitable distribution of health and community resources.

Rowland, C., Fried-Oken, M., Bowser, G., Granlund, M., Lollar, D., Phelps, R., et al. (2016). The communication supports inventory-children & youth (CSI-CY), a new instrument based on the ICF-CY. *Disability and Rehabilitation,* , 1-9.

PURPOSE: Two studies are presented that evaluated the Communication Supports Inventory-Children & Youth (CSI-CY), an instrument designed to facilitate the development of communication-related educational goals for students with complex communication needs (CCN). The CSI-CY incorporates a code set based on the ICF-CY. The studies were designed to determine the effect of using the CSI-CY on IEP goals for students with CCN and to evaluate consumer satisfaction. METHOD: In Study 1, sixty-one educators and speech-language pathologists were randomly assigned to either (a) provide a student's current IEP (control group) or (b) complete the CSI-CY prior to preparing a student's next IEP and to submit the new IEP (experimental group). Study 2 was a field test to generate consumer satisfaction data. RESULTS: Study 1 showed that IEP goals submitted by participants in the experimental group referenced CSI-CY-related content significantly more frequently than did those submitted by control participants. Study 2 revealed high satisfaction with the instrument. CONCLUSIONS: The code set basis of the CSI-CY extends the common language of the ICF-CY to practical educational use for children with CCN across diagnostic groups. The CSI-CY is well regarded as an instrument to inform the content of communication goals related to CCN. Implications for Rehabilitation The CSI-CY will guide rehabilitation professionals to develop goals for children with complex communication impairments. The CSI-CY is a new instrument that is based on the ICF-CY for documentation of communication goals.

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Rudwaleit, M., Rosenbaum, J. T., Landewe, R., Marzo-Ortega, H., Sieper, J., van der Heijde, D., et al. (2016). Observed incidence of uveitis following certolizumab pegol treatment in patients with axial spondyloarthritis. *Arthritis Care & Research,*

OBJECTIVE: Axial spondyloarthritis (axSpA), characterized by inflammation of the spine and sacroiliac joints, can also affect extra-articular sites: the most common manifestation being uveitis. Here we report incidence of uveitis flares in axSpA patients from the RAPID-axSpA trial, including ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA. METHODS: RAPID-axSpA (NCT01087762) is double-blind and placebo (PBO)-controlled to Wk24, dose-blind to Wk48, open-label to Wk204. Patients were randomized to certolizumab pegol (CZP) or PBO. PBO patients entering dose-blind phase were re-randomized to CZP. Uveitis events were recorded on extra-articular manifestation or adverse event forms. Events were analyzed in patients with/without history of uveitis, and rates reported per 100 patient-years (PY). RESULTS: At baseline, 38/218 (17.4%) CZP-randomized and 31/107 (29.0%) PBO-randomized patients had past uveitis history. During the 24-wk double-blind phase, the rate of uveitis flares was lower in CZP (3.0 [0.6-8.8]/100 PY) than PBO (10.3 [2.8-26.3]/100 PY). All cases observed during the 24-wk double-blind phase were in patients with a history of uveitis; in these patients, rates were

similarly lower for CZP (17.1 [3.5-50.1]/100 PY) than PBO (38.5 [10.5-98.5]/100 PY). Rates of uveitis flares remained low up to Wk96 (4.9 [3.2-7.4]/100 PY) and were similar between AS (4.4 [2.3-7.7]/100 PY) and nr-axSpA (5.6 [2.9-9.8]/100 PY). CONCLUSION: The rate of uveitis flares was lower for axSpA patients treated with CZP than PBO during the randomized controlled phase. Incidence of uveitis flares remained low to Wk96 and was comparable to rates reported for AS patients receiving other anti-TNF antibodies. This article is protected by copyright. All rights reserved.

Ruhland, M. K., Coussens, L. M., & Stewart, S. A. (2015). Senescence and cancer: An evolving inflammatory paradox. *Biochimica Et Biophysica Acta - Reviews on Cancer,*

The senescent phenotype was first described in 1961 as a phenomenon characterized by the cessation of cellular division. After years of debate as to whether it represented a tissue culture artifact or an important biological process, it is now appreciated that senescence plays an important role in tumorigenesis. Further, senescence is integral to normal biological processes such as embryogenesis and the maintenance of tissue homeostasis. Now with defined roles in development, wound healing, tumor promotion and tumor suppression, it is not surprising that attention has turned to refining our understanding of the mechanisms behind, and consequences of, the induction of senescence. One emerging role for senescence lies in the ability of senescence to orchestrate an inflammatory response: factors secreted by senescent cells have been identified in multiple contexts to modulate various aspects of the immune response. As with many of the previously described roles for senescence, the type of inflammation established by the senescence phenotype is varied and dependent on context. In this review, we discuss the current state of the field with a focus on the paradoxical outcomes of the senescence-induced inflammatory responses in the context of cancer. A more complete understanding of senescence and an appreciation for its complexities will be important for eventual development of senescence-targeted therapies. © 2015 Elsevier B.V.

Saitz, T. R., Hannan, J. L., Marson, L., Krychman, M., Hartzell-Cushanick, R., Bergeron, S., et al. (2015). Survey of the literature december 2015. *Sexual Medicine, 3*(4), 227-234.

Sajisevi, M. B., Kaylie, D. M., & Weissman, J. L. (2014). Hearing loss and tinnitus. (pp. 359-369) Cambridge University Press.

Acute hearing loss may be evidence of localized (temporal bone) or systemic disease [1]. Acute tinnitus as an isolated presentation is very rare. However, hearing loss and (non-pulsatile) tinnitus are so closely intertwined that consideration of one merits consideration of the other. In this chapter we will show the intimate relationship between hearing loss, both sensorineural and conductive, with tinnitus. The presentation of hearing loss and tinnitus is a completely subjective experience. There is often no outward, objective manifestation of inner-ear dysfunction other than patients' reports. For this reason, the acute nature of the start of symptoms is somewhat dependent on patient reporting. This chapter will describe many entities that can lead to hearing loss and/or tinnitus, and we will describe the likelihood of presentation as an acute symptom. Several of these processes are very likely to present immediately with inner-ear symptoms, and others may be less likely to have inner-ear symptoms as the acute presentation; however, they all should remain in the differential diagnosis. Hearing loss and tinnitus: Background Hearing loss (HL) is either unilateral or bilateral. Bilateral HL may be asymmetric [2]. The division of both acute and chronic HL into sensorineural hearing loss (SNHL) and conductive hearing loss (CHL) focuses the search for an etiology. Tinnitus is the perception of auditory sensation, often in the absence of external stimuli [3, 4]. Tinnitus is classified as pulsatile (synchronous with heartbeat) and non-pulsatile (continuous), and further classified as subjective (perceived by the patient only) and objective (perceived by the examiner as well as by the patient) [2]. Tinnitus may be unilateral or bilateral.

Saks, K., Enestvedt, B. K., Holub, J. L., & Lieberman, D. (2016). Colonoscopy identifies increased prevalence of large polyps or tumors in patients 40-49 years old with hematochezia vs other gastrointestinal indications. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association,*

BACKGROUND & AIMS: There is an unclear role for colonoscopy in evaluation of symptomatic individuals younger than 50 years old. We aimed to determine the prevalence of large polyps (>9 mm) or tumors in individuals 40-49 years old who underwent colonoscopy for various signs and symptoms, and compare the results with those from average-risk individuals age 50-54 years old

who underwent screening colonoscopy. METHODS: We collected data from a national endoscopy database, 2000 through 2012, and identified patients 40-49 years old who underwent colonoscopy for bleeding and nonbleeding indications. The prevalence of large polyps (>9 mm) or tumors was compared to the prevalence in a reference group (n=99,713 average-risk individuals age 50 to 54 undergoing screening colonoscopy). RESULTS: A total of 65,892 patients 40-49 years old underwent colonoscopy for a variety of indications. Significantly larger proportions of male and female patients with hematochezia without anemia or iron deficiency anemia (IDA) had large polyps or tumors (7.2%) compared to the reference group (men: 7.2% vs 6.2%; P=.0001 and women: 5.5% vs 4.1%; P<.0001). Patients with weight loss, anemia or IDA, or hematochezia with anemia or IDA did not have a significantly higher prevalence of large polyps or tumors than the reference group. Significantly lower proportions of patients with general gastrointestinal symptoms (pain, bloating, or change in bowel habits) had advanced neoplasia compared to the reference group (men: 3.9% vs 6.2%; P<.0001 and women: 2.7% vs 4.1%; P<.0001). CONCLUSIONS: An analysis of a national endoscopy database supports the role of colonoscopy to evaluate hematochezia in patients 40-49 years old. A lower proportion of patients with anemia, weight loss, and general abdominal symptoms had large polyps or tumors compared to average-risk patients, 50-54 years old. A significantly lower proportion of patients younger than 50 years with general gastrointestinal symptoms had large polyps-these patients are therefore less likely to benefit from colonoscopy.

Salehi, S., Cooper, P., Smith, A., & Ferracane, J. (2015). Dentin matrix components extracted with phosphoric acid enhance cell proliferation and mineralization. *Dental Materials,*
Objective: Acids, such as those used in adhesive dentistry, have been shown to solubilize bioactive molecules from dentin. These dentin matrix components (DMC) may promote cell proliferation and differentiation, and ultimately contribute to dentin regeneration.The objective of this study was to evaluate the potential for varying concentrations of DMC extracted from human dentin by phosphoric acid of a range of pHs to stimulate proliferation and mineralization of two different cultured pulp cell populations. Methods: DMC were solubilized from powdered human dentin (7 days - 4°C) by phosphoric acid of pH 1, 3, and 5 and also, EDTA. Extracts were dialyzed for 7 days against distilled water and lyophilized. Undifferentiated mouse dental pulp cells (OD-

21) and cells of the odontoblast-like cell line (MDPC-23) were seeded in six-well plates (1×105) and cultured for 24h in DMEM (Dulbecco's modified Eagle's medium) containing 10% (v/v) FBS (fetal bovine serum). The cells were washed with serum-free medium and then treated with different concentrations of DMC (0.01, 0.1, 1.0 and 10.0μg/ml) daily in serum free medium for 7 days. After 3, 5 (MDPC-23 only), and 7 days of treatment, cell proliferation was measured using 10vol% Alamar blue solution, which was added to each well for 1h. Cell numbers were first measured by cell counting (Trypan blue; n =5) and Alamar blue fluorescence to validate the assay, which was then used for the subsequent assessments of proliferation. Mineralization was assessed by Alizarin Red S assay after 12 days exposure to DMC (n =5). Controls were media-only (DMEM) and dexamethasone (DEX; positive control). Results were analysed by ANOVA/Tukey's ($p \leq 0.05$). Results: There was a linear correlation between cell counts and Alamar blue fluorescence ($R^2 > 0.96$ for both cell types) , verifying the validity of the Alamar blue assay for these cell types. In general, there was a dose-dependent trend for enhanced cell proliferation with higher concentration of DMC for both cell lines, especially at 10.0μg/ml. DEX exposure resulted in significantly higher mineralization, but did not affect cell proliferation. DMC exposure demonstrated significantly greater mineralization than media-only control for 10μg/ml for all extracts, and at lower concentrations for EDTA and pH 5 extracts. Significance: Human dentin matrix components solubilized by acids at pH levels found in commercial dentin adhesives enhanced cell proliferation and mineralization of mouse and rat undifferentiated dental pulp cells when presented in adequate concentration.

Salipante, S. J., Adey, A., Thomas, A., Lee, C., Liu, Y. J., Kumar, A., et al. (2016). Recurrent somatic loss of TNFRSF14 in classical hodgkin lymphoma. *Genes Chromosomes and Cancer, 55*(3), 278-287.

Investigation of the genetic lesions underlying classical Hodgkin lymphoma (CHL) has been challenging due to the rarity of Hodgkin and Reed-Sternberg (HRS) cells, the pathognomonic neoplastic cells of CHL. In an effort to catalog more comprehensively recurrent copy number alterations occurring during oncogenesis, we investigated somatic alterations involved in CHL using whole-genome sequencing-mediated copy number analysis of purified HRS cells. We performed low-coverage sequencing of small numbers of intact HRS cells and paired non-

neoplastic B lymphocytes isolated by flow cytometric cell sorting from 19 primary cases, as well as two commonly used HRS-derived cell lines (KM-H2 and L1236). We found that HRS cells contain strikingly fewer copy number abnormalities than CHL cell lines. A subset of cases displayed nonintegral chromosomal copy number states, suggesting internal heterogeneity within the HRS cell population. Recurrent somatic copy number alterations involving known factors in CHL pathogenesis were identified (REL, the PD-1 pathway, and TNFAIP3). In eight cases (42%) we observed recurrent copy number loss of chr1:2,352,236-4,574,271, a region containing the candidate tumor suppressor TNFRSF14. Using flow cytometry, we demonstrated reduced TNFRSF14 expression in HRS cells from 5 of 22 additional cases (23%) and in two of three CHL cell lines. These studies suggest that TNFRSF14 dysregulation may contribute to the pathobiology of CHL in a subset of cases.

Saunders, G. H., Frederick, M. T., Silverman, S. C., Nielsen, C., & Laplante-Levesque, A. (2016). Description of adults seeking hearing help for the first time according to two health behavior change approaches: Transtheoretical model (stages of change) and health belief model. *Ear and Hearing,*

OBJECTIVES: Several models of health behavior change are commonly used in health psychology. This study applied the constructs delineated by two models-the transtheoretical model (in which readiness for health behavior change can be described with the stages of precontemplation, contemplation and action) and the health belief model (in which susceptibility, severity, benefits, barriers, self-efficacy, and cues to action are thought to determine likelihood of health behavior change)-to adults seeking hearing help for the first time. DESIGN: One hundred eighty-two participants (mean age: 69.5 years) were recruited following an initial hearing assessment by an audiologist. Participants' mean four-frequency pure-tone average was 35.4 dB HL, with 25.8% having no hearing impairment, 50.5% having a slight impairment, and 23.1% having a moderate or severe impairment using the World Health Organization definition of hearing loss. Participants' hearing-related attitudes and beliefs toward hearing health behaviors were examined using the University of Rhode Island Change Assessment (URICA) and the health beliefs questionnaire (HBQ), which assess the constructs of the transtheoretical model and the health belief model, respectively. Participants also provided demographic information, and

completed the hearing handicap inventory (HHI) to assess participation restrictions, and the psychosocial impact of hearing loss (PIHL) to assess the extent to which hearing impacts competence, self-esteem, and adaptability. RESULTS: Degree of hearing impairment was associated with participation restrictions, perceived competence, self-esteem and adaptability, and attitudes and beliefs measured by the URICA and the HBQ. As degree of impairment increased, participation restrictions measured by the HHI, and impacts of hearing loss, as measured by the PIHL, increased. The majority of first-time help seekers in this study were in the action stage of change. Furthermore, relative to individuals with less hearing impairment, individuals with more hearing impairment were at more advanced stages of change as measured by the URICA (i.e., higher contemplation and action scores relative to their precontemplation score), and they perceived fewer barriers and more susceptibility, severity, benefits and cues to action as measured by the HBQ. Multiple regression analyses showed participation restrictions (HHI scores) to be a highly significant predictor of stages of change explaining 30% to 37% of the variance, as were duration of hearing difficulty, and perceived benefits, severity, self-efficacy and cues to action assessed by the HBQ. CONCLUSIONS: The main predictors of stages of change in first-time help seekers were reported participation restrictions and duration of hearing difficulty, with constructs from the health belief model also explaining some of the variance in stages of change scores. The transtheoretical model and the health belief model are valuable for understanding hearing health behaviors and can be applied when developing interventions to promote help seeking.

Schafermeyer, E. R., Wan, E. A., Samin, S., Zentzis, N., Preiser, N., Condon, J., et al. (2015). Multi-resident identification using device-free IR and RF fingerprinting. *37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2015, , 2015-November.* pp. 5481-5484.

Remote monitoring of health and mobility is critical in the support of aging-in-place for seniors. However, it is challenging to passively monitor individuals in multi-resident homes. In this paper we present a new method for the identification of individuals using simple wall-mounted radio frequency (RF) transceivers and IR sensors with fingerprinting techniques. The approach is passive or device-free in that it does not require the person being identified to wear any

transmitting device Classification is achieved using features derived from measuring the disruption of RF received signal strength (RSS) among 4 transceivers positioned across either a hallway or doorframe. Three IR sensors provide timing information. Results are given for 3 test subjects (1 female, 2 males). The approach achieves over 98% classification accuracy in distinguishing the female from the male subjects and over 83% in distinguishing between the males using a Gaussian Mixture Model for classification. More than 2300 labeled examples per subject were used for training. When the training data is reduced to less than 140 examples per subject, 96% and 82% classification accuracy is still achieved respectively. © 2015 IEEE.

Schiff, N. D. (2015). Cognitive motor dissociation following severe brain injuries. *JAMA Neurology, 72*(12), 1413-1415.

Schuitevoerder, D., Fortino, J., & Vetto, J. T. (2016). Hard copy durable patient cancer education materials: Do they still matter? *Journal of Cancer Education : The Official Journal of the American Association for Cancer Education,*

Traditional hard copy information materials are still present in our cancer clinics. While their actual impact on patient care often goes un-assessed, it is important to understand their role in today's electronic age where information can easily be obtained from various sources. It has remained the practice in our melanoma clinic to provide an information booklet to all of our new patients. The purpose of this study was to evaluate how useful this booklet was, as well as determine the current resources our patients use to gather cancer information. All patients referred to the clinic in the previous 3 years were pooled from our prospective, IRB-approved, melanoma sentinel node database. Of these 205 patients, a valid email address was listed for 147. A ten-question survey was emailed to all of these patients, who were not told ahead of time that their experience with the booklet would be studied. Seventy-seven of the 147 (52 %) patients polled responded. Fifty-eight (75 %) remembered receiving the booklet at their initial consultation. Forty-four (76 %) of those patients rated it as extremely or very useful, and no patients reported the booklet as not useful at all. Eighty-eight percent of respondents found the information to be clear and helpful. Sixty-four percent remembered the provider reviewing the material with them, and nearly all of these patients found that helpful. When asked to rank the

importance of the various resources for obtaining cancer information, providers were ranked as most important, followed by the information booklet and Internet information sites. Internet blogs and friends and family were rated as the least important sources of information. Even in the current electronic age, our results indicate that information shared by providers, including the hard copy education booklet, was the most important source of information for our newly referred melanoma patients.

Schulze, A., Bauman, M., Tsai, A. C. -., Reynolds, A., Roberts, W., Anagnostou, E., et al. (2016). Prevalence of creatine deficiency syndromes in children with nonsyndromic autism. *Pediatrics, 137*(1)

BACKGROUND AND OBJECTIVE: Creatine deficiency may play a role in the neurobiology of autism and may represent a treatable cause of autism. The goal of the study was to ascertain the prevalence of creatine deficiency syndromes (CDSs) in children with autism spectrum disorder (ASD). Methods: In a prospective multicenter study, 443 children were investigated after a confirmed diagnosis of ASD. Random spot urine screening for creatine metabolites (creatine, guanidinoacetate, creatinine, and arginine) with liquid chromatography-tandem mass spectrometry and second-tier testing with high-performance liquid chromatography methodology was followed by recall testing in 24-hour urines and confirmatory testing by Sanger-based DNA sequencing of GAMT, GATM, and SLC6A8 genes. Additional diagnostic tests included plasma creatine metabolites and in vivo brain proton magnetic resonance spectroscopy. The creatine metabolites in spot urine in the autism group were compared with 128 healthy controls controlled for age. Results: In 443 subjects with ASD investigated for CDS, we had 0 events (event: 0, 95% confidence interval 0-0.0068), therefore with 95% confidence the prevalence of CDS is .0125) in urine. CONCLUSION Our study revealed a very low prevalence of CDS in children with nonsyndromic ASD and no obvious association between creatine metabolites and autism. Unlike our study population, we expect more frequent CDS among children with severe developmental delay, speech impairment, seizures, and movement disorders in addition to impairments in social communication, restricted interests, and repetitive behaviors.

Sciubba, D. M., Yurter, A., Smith, J. S., Kelly, M. P., Scheer, J. K., Goodwin, C. R., et al. (2015). A comprehensive review of complication rates after surgery for adult deformity: A reference for informed consent. *Spine Deformity, 3*(6), 575-594.

Objective An up-to-date review of recent literatures and a comprehensive reference for informed consent specific to ASD complications is lacking. The goal of the present study was to determine current complication rates after ASD surgery, in order to provide a reference for informed consent as well as to determine differences between three-column and non-three-column osteotomy procedures to aid in shared decision making. Methods A review of the literature was conducted using the PubMed database. Randomized controlled trials, nonrandomized trials, cohort studies, case-control studies, and case series providing postoperative complications published in 2000 or later were included. Complication rates were recorded and calculated for perioperative (both major and minor) and long-term complication rates. Postoperative outcomes were all stratified by surgical procedure (ie, three-column osteotomy and non-three-column osteotomy). Results Ninety-three articles were ultimately eligible for analysis. The data of 11,692 patients were extracted; there were 3,646 complications, mean age at surgery was 53.3 years (range: 25-77 years), mean follow-up was 3.49 years (range: 6 weeks-9.7 years), estimated blood loss was 2,161 mL (range: 717-7,034 mL), and the overall mean complication rate was 55%. Specifically, major perioperative complications occurred at a mean rate of 18.5%, minor perioperative complications occurred at a mean rate of 15.7%, and long-term complications occurred at a mean rate of 20.5%. Furthermore, three-column osteotomy resulted in a higher overall complication rate and estimated blood loss than non-three-column osteotomy. Conclusions A review of recent literatures providing complication rates for ASD surgery was performed, providing the most up-to-date incidence of early and late complications. Providers may use such data in helping to counsel patients of the literature-supported complication rates of such procedures despite the planned benefits, thus obtaining a more thorough informed consent. © 2015 Scoliosis Research Society.

Scoles, D., Flatter, J. A., Cooper, R. F., Langlo, C. S., Robison, S., Neitz, M., et al. (2016). Assessing photoreceptor structure associated with ellipsoid zone disruptions visualized with optical coherence tomography. *Retina, 36*(1), 91-103.

Purpose: To compare images of photoreceptor layer disruptions obtained with optical coherence tomography (OCT) and adaptive optics scanning light ophthalmoscopy (AOSLO) in a variety of pathologic states. Methods: Five subjects with photoreceptor ellipsoid zone disruption as per OCT and clinical diagnoses of closed-globe blunt ocular trauma (n = 2), macular telangiectasia type 2 (n = 1), blue-cone monochromacy (n = 1), or cone-rod dystrophy (n = 1) were included. Images were acquired within and around photoreceptor lesions using spectral domain OCT, confocal AOSLO, and split-detector AOSLO. Results: There were substantial differences in the extent and appearance of the photoreceptor mosaic as revealed by confocal AOSLO, split-detector AOSLO, and spectral domain OCT en face view of the ellipsoid zone. Conclusion: Clinically available spectral domain OCT, viewed en face or as B-scan, may lead to misinterpretation of photoreceptor anatomy in a variety of diseases and injuries. This was demonstrated using split-detector AOSLO to reveal substantial populations of photoreceptors in areas of no, low, or ambiguous ellipsoid zone reflectivity with en face OCT and confocal AOSLO. Although it is unclear if these photoreceptors are functional, their presence offers hope for therapeutic strategies aimed at preserving or restoring photoreceptor function.

Seo, J. -., Jones, S. M., Hostetter, T. A., Iliff, J. J., & West, G. A. (2016). Methamphetamine induces the release of endothelin. *Journal of Neuroscience Research, 94*(2), 170-178.

Methamphetamine is a potent psychostimulant drug of abuse that increases release and blocks reuptake of dopamine, producing intense euphoria, factors that may contribute to its widespread abuse. It also produces severe neurotoxicity resulting from oxidative stress, DNA damage, blood-brain barrier disruption, microgliosis, and mitochondrial dysfunction. Intracerebral hemorrhagic and ischemic stroke have been reported after intravenous and oral abuse of methamphetamine. Several studies have shown that methamphetamine causes vasoconstriction of vessels. This study investigates the effect of methamphetamine on endothelin-1 (ET-1) release in mouse brain endothelial cells by ELISA. ET-1 transcription as well as endothelial nitric oxide synthase (eNOS) activation and transcription were measured following methamphetamine treatment. We also examine the effect of methamphetamine on isolated cerebral arteriolar vessels from C57BL/6 mice. Penetrating middle cerebral arterioles were cannulated at both ends with a micropipette system. Methamphetamine was applied extraluminally, and the vascular response was

investigated. Methamphetamine treatment of mouse brain endothelial cells resulted in ET-1 release and a transient increase in ET-1 message. The activity and transcription of eNOS were only slightly enhanced after 24hr of treatment with methamphetamine. In addition, methamphetamine caused significant vasoconstriction of isolated mouse intracerebral arterioles. The vasoconstrictive effect of methamphetamine was attenuated by coapplication of the endothelin receptor antagonist PD145065. These findings suggest that vasoconstriction induced by methamphetamine is mediated through the endothelin receptor and may involve an endothelin-dependent pathway. © 2016 Wiley Periodicals, Inc.

Shaath, T., Fischer, R., Goeser, M., Rajpara, A., & Aires, D. (2016). Scurvy in the present times: Vitamin c allergy leading to strict fast food diet. *Dermatology Online Journal, 22*(1)
Scurvy results from a deficiency of vitamin C, a nutrient otherwise known as ascorbic acid. Today, scurvy is rare yet emerges in select patients. The patient reported herein developed scurvy secondary to deliberate avoidance of vitamin C-rich foods. Classic cutaneous manifestations of scurvy include follicular hyperkeratosis and perifollicular hemorrhage encompassing coiled "corkscrew" hairs and hairs bent into "swan-neck" deformities. Ecchymoses, purpura, and petechiae are also characteristically prominent. Classic oral abnormalities include erythematous, swollen gingivae that hemorrhage from subtle microtrauma. Subungual linear splinter hemorrhages may also manifest as a sign of the disease. To establish the diagnosis requirements include characteristic physical exam findings, evidence of inadequate dietary intake, and rapid reversal of symptoms upon supplementation. Although unnecessary for diagnosis, histological findings demonstrate perifollicular inflammation and hemorrhage, fibrosis, and hyperkeratosis, amongst dilated hair follicles and keratin plugging. Although citrus fruit allergies have been historically documented, ascorbic acid has not been previously reported as an allergen. Although lacking absolute certainty, this report suggests a presumed case of ascorbic acid allergy based on patient history and favorable response to ascorbic acid desensitization therapy. © 2016 by the article author(s).

Shaw, A. T., Gandhi, L., Gadgeel, S., Riely, G. J., Cetnar, J., West, H., et al. (2015). Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: A single-group, multicentre, phase 2

trial. *The Lancet Oncology,*

Background: Alectinib-a highly selective, CNS-active, ALK inhibitor-showed promising clinical activity in crizotinib-naive and crizotinib-resistant patients with ALK-rearranged (ALK-positive) non-small-cell lung cancer (NSCLC). We aimed to assess the safety and efficacy of alectinib in patients with ALK-positive NSCLC who progressed on previous crizotinib. Methods: We did a phase 2 study at 27 centres in the USA and Canada. We enrolled patients aged 18 years or older with stage IIIB-IV, ALK-positive NSCLC who had progressed after crizotinib. Patients were treated with oral alectinib 600 mg twice daily until progression, death, or withdrawal. The primary endpoint was the proportion of patients achieving an objective response by an independent review committee using Response Evaluation Criteria in Solid Tumors, version 1.1. Response endpoints were assessed in the response-evaluable population (ie, patients with measurable disease at baseline who received at least one dose of study drug), and efficacy and safety analyses were done in the intention-to-treat population (all enrolled patients). This study is registered with ClinicalTrials.gov, number NCT01871805. The study is ongoing and patients are still receiving treatment. Findings: Between Sept 4, 2013, and Aug 4, 2014, 87 patients were enrolled into the study (intention-to-treat population). At the time of the primary analysis (median follow-up 4·8 months [IQR 3·3-7·1]), 33 of 69 patients with measurable disease at baseline had a confirmed partial response; thus, the proportion of patients achieving an objective response by the independent review committee was 48% (95% CI 36-60). Adverse events were predominantly grade 1 or 2, most commonly constipation (31 [36%]), fatigue (29 [33%]), myalgia 21 [24%]), and peripheral oedema 20 [23%]). The most common grade 3 and 4 adverse events were changes in laboratory values, including increased blood creatine phosphokinase (seven [8%]), increased alanine aminotransferase (five [6%]), and increased aspartate aminotransferase (four [5%]). Two patients died: one had a haemorrhage (judged related to study treatment), and one had disease progression and a history of stroke (judged unrelated to treatment). Interpretation: Alectinib showed clinical activity and was well tolerated in patients with ALK-positive NSCLC who had progressed on crizotinib. Therefore, alectinib could be a suitable treatment for patients with ALK-positive disease who have progressed on crizotinib. Funding: F Hoffmann-La Roche.

Sheridan, D. C., Sheridan, J., Johnson, K. P., Laurie, A., Knapper, A., Fu, R., et al. (2016). The effect of a dedicated psychiatric team to pediatric emergency mental health care. *The Journal of Emergency Medicine,*

BACKGROUND: Pediatric emergency department (PED) visits among children and adolescents with acute mental health needs have increased over the past decade with long wait times in the PED awaiting disposition. OBJECTIVE: The objective of this study was to evaluate the effect of a new pediatric mental health liaison program with the hypothesis that this model reduces length of stay (LOS) and hospitalization rates among pediatric mental health patients. METHODS: This was a pre- and postintervention retrospective study of the year prior to (June 2012-June 2013) and the year after (October 2013-October 2014) implementation of a new PED psychiatric team. All patients aged 1-18 years with a mental health International Classification of Diseases-9th Revision code were included. Patients who did not receive a Psychiatry consult in the PED were excluded. RESULTS: There were 83 encounters in the year prior to and 129 encounters in the year after the implementation of the liaison program. There was an increase in the suicidality of mental health patients during this time. There was a significant decrease in mean PED LOS of 27% (95% confidence interval [CI] 0-46%; $p = 0.05$) from pre- to postintervention period. The decrease in the proportion of patients admitted/transferred to an inpatient psychiatric facility in the postintervention year was statistically significant (odds ratio 0.35; 95% CI 0.17-0.71; $p < 0.01$). CONCLUSIONS: The use of a dedicated child psychiatrist and mental health social worker to the PED results in significantly decreased LOS and need for admission without any change in return visit rate. Larger, multicenter studies are needed to confirm these findings.

Shi, X. (2016). Pathophysiology of the cochlear intrastrial fluid-blood barrier (review). *Hearing Research,*

The blood-labyrinth barrier (BLB) in the stria vascularis is a highly specialized capillary network that controls exchanges between blood and the intrastitial space in the cochlea. The barrier shields the inner ear from blood-born toxic substances and selectively passes ions, fluids, and nutrients to the cochlea, playing an essential role in the maintenance of cochlear homeostasis. Anatomically, the BLB is comprised of endothelial cells (ECs) in the strial microvasculature, elaborated tight and adherens junctions, pericytes (PCs), basement membrane (BM), and

perivascular resident macrophage-like melanocytes (PVM/Ms), which together form a complex "cochlear-vascular unit" in the stria vascularis. Physical interactions between the ECs, PCs, and PVM/Ms, as well as signaling between the cells, is critical for controlling vascular permeability and providing a proper environment for hearing function. Breakdown of normal interactions between components of the BLB is seen in a wide range of pathological conditions, including genetic defects and conditions engendered by inflammation, loud sound trauma, and ageing. In this review, we will discuss prevailing views of the structure and function of the strial cochlear-vascular unit (also referred to as the "intrastrial fluid-blood barrier"). We will also discuss the disrupted homeostasis seen in a variety of hearing disorders. Therapeutic targeting of the strial barrier may offer opportunities for improvement of hearing health and amelioration of auditory disorders.

Shinto, L., Marracci, G., Mohr, D. C., Bumgarner, L., Murchison, C., Senders, A., et al. (2016). Omega-3 fatty acids for depression in multiple sclerosis: A randomized pilot study. *PloS One, 11*(1), e0147195.
TRIAL REGISTRATION: ClinicalTrials.gov NCT00122954.

Sihag, S., Kosinski, A. S., Gaissert, H. A., Wright, C. D., & Schipper, P. H. (2015). Minimally invasive versus open esophagectomy for esophageal cancer: A comparison of early surgical outcomes from the society of thoracic surgeons national database. *Annals of Thoracic Surgery,*
Background: Open esophagectomy results in significant morbidity and mortality. Minimally invasive esophagectomy (MIE) has become increasingly popular at specialized centers with the aim of improving perioperative outcomes. Numerous single-institution studies suggest MIE may offer lower short-term morbidity. The two approaches are compared using a large, multiinstitutional database. Methods: The Society of Thoracic Surgeons (STS) National Database (v2.081) was queried for all resections performed for esophageal cancer between 2008 and 2011 (n = 3,780). Minimally invasive approaches included both transhiatal (n = 214) and Ivor Lewis (n = 600), and these were compared directly with open transhiatal (n = 1,065) and Ivor Lewis (n = 1,291) procedures, respectively. Thirty-day outcomes were examined using nonparametric statistical testing. Results: Both open and MIE groups were similar in terms of preoperative risk

factors. Morbidity and all-cause mortality were equivalent at 62.2% and 3.8%. MIE was associated with longer median procedure times (443.0 versus 312.0 minutes; $p < 0.001$), but a shorter median length of hospital stay (9.0 versus 10.0 days; $p < 0.001$). Patients who underwent MIE had higher rates of reoperation (9.9% versus 4.4%; $p < 0.001$) and empyema (4.1% versus 1.8%; $p < 0.001$). Open technique led to an increased rate of wound infections (6.3% versus 2.3%; $p < 0.001$), postoperative transfusion (18.7% versus 14.1%; $p = 0.002$), and ileus (4.5% versus 2.2%; $p = 0.002$). Propensity score-matched analysis confirmed these findings. High- and low-volume centers had similar outcomes. Conclusions: Early results from the STS National Database indicate that MIE is safe, with comparable rates of morbidity and mortality as open technique. Longer procedure times and a higher rate of reoperation following MIE may reflect a learning curve.

Silverman, S., Agodoa, I., Kruse, M., Parthan, A., & Orwoll, E. (2015). Denosumab for elderly men with osteoporosis: A cost-effectiveness analysis from the US payer perspective. *Journal of Osteoporosis, 2015*

Purpose. To evaluate the cost-effectiveness of denosumab versus other osteoporotic treatments in older men with osteoporosis from a US payer perspective. Methods. A lifetime cohort Markov model previously developed for postmenopausal osteoporosis (PMO) was used. Men in the model were 78 years old, with a BMD T-score of -2.12 and a vertebral fracture prevalence of 23%. During each 6-month Markov cycle, patients could have experienced a hip, vertebral or nonhip, nonvertebral (NHNV) osteoporotic fracture, remained in a nonfracture state, remained in a postfracture state, or died. Background fracture risks, mortality rates, persistence rates, health utilities, and medical and drug costs were derived from published sources. Previous PMO studies were used for drug efficacy in reducing fracture risk. Lifetime expected costs and quality-adjusted life-years (QALYs) were estimated for denosumab, generic alendronate, risedronate, ibandronate, teriparatide, and zoledronate. Results. Denosumab had an incremental cost-effectiveness ratio (ICER) of $16,888 compared to generic alendronate and dominated all other treatments. Results were most sensitive to changes in costs of denosumab and the relative risk of hip fracture. Conclusion. Despite a higher annual treatment cost compared to other medications, denosumab

is cost-effective compared to other osteoporotic treatments in older osteoporotic US men. © 2015 Stuart Silverman et al.

Simpson, E. L., Bieber, T., Eckert, L., Wu, R., Ardeleanu, M., Graham, N. M. H., et al. (2015). Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *Journal of the American Academy of Dermatology,*

Background: The adult burden of atopic dermatitis (AD) is poorly characterized. Objective: We sought to characterize AD burden in adults with moderate to severe disease from the patient's perspective. Methods: Patient-reported outcomes collected at screening in a phase 2b clinical trial of dupilumab included pruritus numeric rating scale, 5-Dimension Pruritus Scale, subjective components of SCORing AD, Patient-Oriented Eczema Measure, Hospital Anxiety and Depression Scale, Dermatology Life Quality Index, and 5-Dimension EuroQol. Results: Most of the 380 patients had been living with AD for nearly all their lives, whereas approximately 40% were given a diagnosis as adults; 40.3% had asthma and 60.5% had other allergic conditions. Despite 48.2% of patients using systemic therapies in the past year, patients reported problems with itch frequency (85% of patients), duration (41.5% reported itching ≥18 h/d), and severity (6.5 of 10 on numeric rating scale); 55% reported AD-related sleep disturbances 5 d/wk or more. Hospital Anxiety and Depression Scale scores suggesting clinically relevant anxiety or depression were reported by 21.8% of patients. Quality of life was impaired on Dermatology Life Quality Index and 5-dimension EuroQol. Limitations: This study had limited generalizability; conclusions may not reflect those with mild AD or not participating in a clinical trial. Conclusions: Adults with moderate to severe AD report multidimensional burden including disease activity, patient-reported symptoms, comorbidities, and quality-of-life impact. © 2015 American Academy of Dermatology, Inc.

Slayden, O. D. (2016). Translational in vivo models for women's health: The nonhuman primate endometrium-A predictive model for assessing steroid receptor modulators. *Handbook of Experimental Pharmacology,*

Macaques and baboons display physiological responses to steroid hormones that are similar to those of women. Herein, we describe various uses of nonhuman primates for preclinical studies

on menstruation, endometriosis, and as a model system to evaluate reproductive therapies and contraceptives. Our goal is to outline the strengths of the nonhuman primate model for studies leading to improved therapies for women.

Smith, M. L., Li, J., Cote, D. M., & Ryabinin, A. E. (2016). Effects of isoflurane and ethanol administration on c-fos immunoreactivity in mice. *Neuroscience, 316*, 337-343. Noninvasive functional imaging holds great promise for the future of translational research, due to the ability to directly compare between preclinical and clinical models of psychiatric disorders. Despite this potential, concerns have been raised regarding the necessity to anesthetize rodent and monkey subjects during these procedures, because anesthetics may alter neuronal activity. For example, in studies on drugs of abuse and alcohol, it is not clear to what extent anesthesia can interfere with drug-induced neural activity. Therefore, the current study investigated whole-brain c-Fos activation following isoflurane anesthesia as well as ethanol-induced activation of c-Fos in anesthetized mice. In the first experiment, we examined effects of one or three sessions of gaseous isoflurane on c-Fos activation across the brain in male C57BL/6J mice. Isoflurane administration led to c-Fos activation in several areas, including the piriform cortex and lateral septum. Lower or similar levels of activation in these areas were detected after three sessions of isoflurane, suggesting that multiple exposures may eliminate some of the enhanced neuronal activation caused by acute isoflurane. In the second experiment, we investigated the ability of ethanol injection (1.5 or 2.5g/kgi.p.) to induce c-Fos activation under anesthesia. Following three sessions of isoflurane, 1.5g/kg of ethanol induced c-Fos in the central nucleus of amygdala and the centrally-projecting Edinger-Westphal nucleus (EWcp). This induction was lower after 2.5g/kg of ethanol. These results demonstrate that ethanol-induced neural activation can be detected in the presence of isoflurane anesthesia. They also suggest, that while habituation to isoflurane helps reduce neuronal activation, interaction between effects of anesthesia and alcohol can occur. Studies using fMRI imaging could benefit from using habituated animals and dose-response analyses.

Snowden, J. M., & Caughey, A. B. (2015). Is there a weekend effect in obstetrics? *BMJ (Online), 351*

Snowden, J. M., Tilden, E. L., Snyder, J., Quigley, B., Caughey, A. B., & Cheng, Y. W. (2015). Planned out-of-hospital birth and birth outcomes. *New England Journal of Medicine, 373*(27), 2642-2653. BACKGROUND The frequency of planned out-of-hospital birth in the United States has increased in recent years. The value of studies assessing the perinatal risks of planned outof- hospital birth versus hospital birth has been limited by cases in which transfer to a hospital is required and a birth that was initially planned as an out-of-hospital birth is misclassified as a hospital birth. METHODS We performed a population-based, retrospective cohort study of all births that occurred in Oregon during 2012 and 2013 using data from newly revised Oregon birth certificates that allowed for the disaggregation of hospital births into the categories of planned in-hospital births and planned out-of-hospital births that took place in the hospital after a woman's intrapartum transfer to the hospital. We assessed perinatal morbidity and mortality, maternal morbidity, and obstetrical procedures according to the planned birth setting (out of hospital vs. hospital). RESULTS Planned out-of-hospital birth was associated with a higher rate of perinatal death than was planned in-hospital birth (3.9 vs. 1.8 deaths per 1000 deliveries, P = 0.003; odds ratio after adjustment for maternal characteristics and medical conditions, 2.43; 95% confidence interval [CI], 1.37 to 4.30; adjusted risk difference, 1.52 deaths per 1000 births; 95% CI, 0.51 to 2.54). The odds for neonatal seizure were higher and the odds for admission to a neonatal intensive care unit lower with planned out-of-hospital births than with planned in-hospital birth. Planned out-of-hospital birth was also strongly associated with unassisted vaginal delivery (93.8%, vs. 71.9% with planned in-hospital births; P<0.001) and with decreased odds for obstetrical procedures. CONCLUSIONS Perinatal mortality was higher with planned out-of-hospital birth than with planned in-hospital birth, but the absolute risk of death was low in both settings. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.) Copyright © 2015 Massachusetts Medical Society.

Soler, Z. M., Hyer, J. M., Rudmik, L., Ramakrishnan, V., Smith, T. L., & Schlosser, R. J. (2016). Cluster analysis and prediction of treatment outcomes for chronic rhinosinusitis. *The Journal of Allergy and Clinical Immunology,*

BACKGROUND: Current clinical classifications of chronic rhinosinusitis (CRS) have weak prognostic utility regarding treatment outcomes. Simplified discriminant analysis based on

unsupervised clustering has identified novel phenotypic subgroups of CRS, but prognostic utility is unknown. OBJECTIVE: We sought to determine whether discriminant analysis allows prognostication in patients choosing surgery versus continued medical management. METHODS: A multi-institutional prospective study of patients with CRS in whom initial medical therapy failed who then self-selected continued medical management or surgical treatment was used to separate patients into 5 clusters based on a previously described discriminant analysis using total Sino-Nasal Outcome Test-22 (SNOT-22) score, age, and missed productivity. Patients completed the SNOT-22 at baseline and for 18 months of follow-up. Baseline demographic and objective measures included olfactory testing, computed tomography, and endoscopy scoring. SNOT-22 outcomes for surgical versus continued medical treatment were compared across clusters. RESULTS: Data were available on 690 patients. Baseline differences in demographics, comorbidities, objective disease measures, and patient-reported outcomes were similar to previous clustering reports. Three of 5 clusters identified by means of discriminant analysis had improved SNOT-22 outcomes with surgical intervention when compared with continued medical management (surgery was a mean of 21.2 points better across these 3 clusters at 6 months, $P < .05$). These differences were sustained at 18 months of follow-up. Two of 5 clusters had similar outcomes when comparing surgery with continued medical management. CONCLUSION: A simplified discriminant analysis based on 3 common clinical variables is able to cluster patients and provide prognostic information regarding surgical treatment versus continued medical management in patients with CRS.

Sonnenberg, A., & Bakis, G. (2016). Probability of iatrogenesis in gastroenterology. *Digestive Diseases and Sciences,* , 1-3.

Spindel, E. R. (2016). Cholinergic targets in lung cancer. *Current Pharmaceutical Design,*

Lung cancers express an autocrine cholinergic loop in which secreted acetylcholine can stimulate tumor growth through both nicotinic and muscarinic receptors. Because activation of mAChR and nAChR stimulates growth; tumor growth can be stimulated by both locally synthesized acetylcholine as well as acetylcholine from distal sources and from nicotine in the high percentage of lung cancer patients who are smokers. The stimulation of lung cancer growth by cholinergic

agonists offers many potential new targets for lung cancer therapy. Cholinergic signaling can be targeted at the level of choline transport; acetylcholine synthesis, secretion and degradation; and nicotinic and muscarinic receptors. In addition, the newly describe family of ly-6 allosteric modulators of nicotinic signaling such as lynx1 and lynx2 offers yet another new approach to novel lung cancer therapeutics. Each of these targets has their potential advantages and disadvantages for the development of new lung cancer therapies which are discussed in this review.

Spindel, E. R., & McEvoy, C. T. (2016). The role of nicotine in the effects of maternal smoking during pregnancy on lung development and childhood respiratory disease: Implications for dangers of E-cigarettes. *American Journal of Respiratory and Critical Care Medicine,*
Use of e-cigarettes, especially among the young is increasing at near exponential rates. This is coupled with a perception that e-cigarettes are safe and with unlimited advertising geared towards vulnerable populations, the groups most likely to smoke or vape during pregnancy. There is now wide appreciation of the dangers of maternal smoking during pregnancy and the life-long consequences this has on offspring lung function, including the increased risk of childhood wheezing and subsequent asthma. Recent evidence strongly supports that much of the effects of smoking during pregnancy on offspring lung function is mediated by nicotine, making it highly likely that e-cigarette use during pregnancy will have the same harmful effects on offspring lung function and health as do conventional cigarettes. In fact, the evidence for nicotine being the mediator of a harm of conventional cigarettes may be most compelling for its effects on lung development. This raises concerns both on the combined use of e-cigarettes plus conventional cigarettes by smokers during pregnancy as well as concerns on the use of e-cigarettes by e-cigarette only users who think them safe or by those sufficiently addicted to nicotine to not be able to quit e-cigarette usage during pregnancy. Thus it is important for health professionals to be aware of the risks of e-cigarette usage during pregnancy particularly as it pertains to offspring respiratory health.

Steele, T. O., Detwiller, K. Y., Mace, J. C., Strong, E. B., Smith, T. L., & Alt, J. A. (2016). Productivity outcomes following endoscopic sinus surgery for recurrent acute rhinosinusitis. *The*

Laryngoscope,

OBJECTIVES/HYPOTHESIS: We sought to evaluate preoperative and postoperative productivity losses and quality of life (QOL) impairment reported by patients with recurrent acute rhinosinusitis (RARS) as compared to patients with chronic rhinosinusitis without nasal polyposis (CRSsNP). STUDY DESIGN: Prospective, multi-institutional, nested case-control. METHODS: Participants with RARS (n = 20) and CRSsNP (n = 20) undergoing endoscopic sinus surgery (ESS) were enrolled as part of a prospective cohort study. For comparison, participants diagnosed with RARS cases were age/gender-matched to control participants diagnosed with CRSsNP using a 1:1 ratio. RESULTS: RARS and CRSsNP participants were followed for approximately 14 months postoperatively. Productivity losses were reported as the number of days missed from normal productive activities out of the previous 90 days. RARS participants reported similar baseline productivity losses (12.6 +/- 27.1 [standard deviation]) as participants with CRSsNP (11.7 +/- 20.9; P = .314). Postoperatively, improvement in productivity losses was similar between RARS participants and CRSsNP controls (-6.7 +/- 20.0 vs. -9.8 +/- 19.1; P = .253). Preoperative and postoperative disease-specific QOL measures (Sino-Nasal Outcomes Test-22 and Rhinosinusitis Disability Index) were similar between the two groups. RARS participants reported a significant decrease in days of previous antibiotic (P = .009) and nasal decongestant (P = .004) use following ESS, whereas participants with CRSsNP reported a significant decrease in antibiotic (P = .002) and oral corticosteroid use (P = .002). CONCLUSIONS: RARS patients report baseline productivity losses and disease-specific QOL impairment to levels that parallel those with CRSsNP. Patients with RARS report improvement in QOL following ESS in all disease-specific QOL measures and in several medication measures. Productivity losses and postoperative improvements are similar between patients with RARS and CRSsNP. LEVEL OF EVIDENCE: 3b Laryngoscope, 2015.

Stevens, C. D., & Simon, J. H. (2014). Acute brain trauma. (pp. 228-248) Cambridge University Press.

This chapter covers the clinical and imaging evaluation of closed head injuries. It focuses primarily on the initial evaluation and management of mild to moderate traumatic brain injury (TBI), as these injuries of lesser severity account for the vast majority of patients confronted by the typical clinician practising in civilian settings. The discussion centers on deceleration-induced

head injuries, those incurred by patients in the setting of unintentional injuries such as falls or motor-vehicle crashes in which the head strikes a hard object with sudden deceleration of the skull and its contents, or intentional injuries in which the head is struck with a blunt object. Penetrating brain injury is not discussed here, as these less-common, generally devastating types of head trauma require specialized imaging and interventions that lie beyond the scope of this book. The discussion emphasizes injuries incurred in civilian settings, and does not cover concussive blast injuries and other combat-related traumatic brain injuries. Newly identified entities such as "chronic traumatic encephalopathy," which may result from repeated minor brain injuries sustained in professional and amateur sports such as football, hockey, and boxing also lie beyond the scope of practice of the typical clinician, require specialized evaluation and treatment, and are not covered here. At least 1.7 million people seek medical attention for a TBI each year in the United States. These injuries result in nearly 1.4 million emergency department (ED) visits, 275 00 hospitalizations, and 52 000 deaths. Approximately three -uarters of these injuries constitute concussions, or other minor TBIs [1]. Worldwide estimates for TBI are about 10 million people affected annually. Although falls account for a majority of ED visits and hospitalizations, motor-vehicle crashes cause the greatest number of fatal TBIs. Falls predominate as the causes of brain injury in children and the elderly, with motor-vehicle crashes causing most brain injuries in working-aged adults [2]. © Cambridge University Press 2014.

Stokbro, K., Aagaard, E., Torkov, P., Bell, R. B., & Thygesen, T. (2016). Surgical accuracy of three-dimensional virtual planning: A pilot study of bimaxillary orthognathic procedures including maxillary segmentation. *International Journal of Oral and Maxillofacial Surgery, 45*(1), 8-18. This retrospective study evaluated the precision and positional accuracy of different orthognathic procedures following virtual surgical planning in 30 patients. To date, no studies of three-dimensional virtual surgical planning have evaluated the influence of segmentation on positional accuracy and transverse expansion. Furthermore, only a few have evaluated the precision and accuracy of genioplasty in placement of the chin segment. The virtual surgical plan was compared with the postsurgical outcome by using three linear and three rotational measurements. The influence of maxillary segmentation was analyzed in both superior and inferior maxillary repositioning. In addition, transverse surgical expansion was compared with the postsurgical

expansion obtained. An overall, high degree of linear accuracy between planned and postsurgical outcomes was found, but with a large standard deviation. Rotational difference showed an increase in pitch, mainly affecting the maxilla. Segmentation had no significant influence on maxillary placement. However, a posterior movement was observed in inferior maxillary repositioning. A lack of transverse expansion was observed in the segmented maxilla independent of the degree of expansion. © 2015 International Association of Oral and Maxillofacial Surgeons.

Su, J. P., Li, Y., Tang, M., Liu, L., Pechauer, A. D., Huang, D., et al. (2015). Imaging the anterior eye with dynamic-focus swept-source optical coherence tomography. *Journal of Biomedical Optics, 20*(12)

A custom-built dynamic-focus swept-source optical coherence tomography (SS-OCT) system with a central wavelength of 1310 nm was used to image the anterior eye from the cornea to the lens. An electrically tunable lens was utilized to dynamically control the positions of focusing planes over the imaging range of 10 mm. The B-scan images were acquired consecutively at the same position but with different focus settings. The B-scan images were then registered and averaged after filtering the out-of-focus regions using a Gaussian window. By fusing images obtained at different depth focus locations, high-resolution and high signal-strength images were obtained over the entire imaging depth. In vivo imaging of human anterior segment was demonstrated. The performance of the system was compared with two commercial OCT systems. The human eye ciliary body was better visualized with the dynamic-focusing SS-OCT system than using the commercial 840 and 1310 nm OCT systems. The sulcus-to-sulcus distance was measured, and the result agreed with that acquired with ultrasound biomicroscopy. © 2015 Society of Photo-Optical Instrumentation Engineers (SPIE).

Swartz, J. E., Aarts, M. C. J., Swart, K. M. A., Disa, J. J., Gerressen, M., Kuo, Y. -., et al. (2015). The value of postoperative anticoagulants to improve flap survival in the free radial forearm flap: A systematic review and retrospective multicentre analysis. *Clinical Otolaryngology, 40*(6), 600-609.

Background: Free radial forearm flap (FRFF) reconstruction is a valuable technique in head and

neck surgery, which allows closure of large defects while striving to maintain functionality. Anticoagulative drugs are often administered to improve flap survival, although evidence regarding effectiveness is lacking. Objective of review: To investigate the effectiveness of postoperative anticoagulants to improve survival of the FRFF in head and neck reconstruction. Type of review: Systematic review and multicentre, individual patient data meta-analysis. Search strategy: MEDLINE, EMBASE, Web of Science and CINAHL were searched for synonyms of 'anticoagulants' and 'free flap reconstruction'. Evaluation method: Studies were critically appraised for directness of evidence and risk of bias. Authors of the highest quality publications were invited to submit their original data for meta-analysis. Results: Five studies were of adequate quality, and data from four studies (80%) were available for meta-analysis, describing 759 FRFF procedures. Anticoagulants used were as follows: aspirin (12%), low molecular weight dextran (18.3%), unfractioned heparin (28.1%), low molecular weight heparin (49%) and prostaglandin-E1 (2.1%). Thirty-one per cent did not receive anticoagulants. Flap failure occurred in 40 of 759 patients (5.3%) On univariate analysis, use of unfractioned heparin was associated with a higher rate of flap failure. However, these regimens were often administered to patients who had revision surgery of the anastomosis. In multivariate logistic regression analysis, anticoagulant use was not associated with improved flap survival or flap-related complications. Conclusions: The studied anticoagulative drugs did not improve FRFF survival or lower the rate of flap-related complications. In addition, some anticoagulants may cause systemic complications.

Takamizawa, T., Barkmeier, W. W., Tsujimoto, A., Berry, T. P., Watanabe, H., Erickson, R. L., et al. (2015). Influence of different etching modes on bond strength and fatigue strength to dentin using universal adhesive systems. *Dental Materials,*

Objectives: The purpose of this study was to determine the dentin bonding ability of three new universal adhesive systems under different etching modes using fatigue testing. Method: Prime & Bond elect [PE] (DENTSPLY Caulk), Scotchbond Universal [SU] (3M ESPE), and All Bond Universal [AU] (Bisco) were used in this study. A conventional single-step self-etch adhesive, Clearfil Bond SE ONE [CS] (Kuraray Noritake Dental) was also included as a control. Shear bond strengths (SBS) and shear fatigue strength (SFS) to human dentin were obtained in the total-etch mode

and self-etch modes. For each test condition, 15 specimens were prepared for the SBS and 30 specimens for SFS. SEM was used to examine representative de-bonded specimens, treated dentin surfaces and the resin/dentin interface for each test condition. Results: Among the universal adhesives, PE in total-etch mode showed significantly higher SBS and SFS values than in self-etch mode. SU and AU did not show any significant difference in SBS and SFS between the total-etch mode and self-etch mode. However, the single-step self-etch adhesive CS showed significantly lower SBS and SFS values in the etch-and-rinse mode when compared to the self-etch mode. Examining the ratio of SFS/SBS, for PE and AU, the etch-and-rinse mode groups showed higher ratios than the self-etch mode groups. Significance: The influence of different etching modes on dentin bond quality of universal adhesives was dependent on the adhesive material. However, for the universal adhesives, using the total-etch mode did not have a negative impact on dentin bond quality. © 2015 Academy of Dental Materials.

Tantravahi, S. K., Szankasi, P., Khorashad, J. S., Dao, K. H., Kovacsovics, T., Kelley, T. W., et al. (2016). A phase II study of the efficacy, safety and determinants of response to 5-azacitidine (vidaza(R)) in patients with chronic myelomonocytic leukemia. *Leukemia & Lymphoma,* , 1-12.

Taylor, B. E., McClave, S. A., Martindale, R. G., Warren, M. M., Johnson, D. R., Braunschweig, C., et al. (2016). Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of critical care medicine (SCCM) and american society for parenteral and enteral nutrition (A.S.P.E.N.). *Critical Care Medicine, 44*(2), 390-438.

Thaçi, D., Simpson, E. L., Beck, L. A., Bieber, T., Blauvelt, A., Papp, K., et al. (2016). Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: A randomised, placebo-controlled, dose-ranging phase 2b trial. *The Lancet, 387*(10013), 40-52.

Background Data from early-stage studies suggested that interleukin (IL)-4 and IL-13 are requisite drivers of atopic dermatitis, evidenced by marked improvement after treatment with dupilumab, a fully-human monoclonal antibody that blocks both pathways. We aimed to assess the efficacy and safety of several dose regimens of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments. Methods In this randomised,

placebo-controlled, double-blind study, we enrolled patients aged 18 years or older who had an Eczema Area and Severity Index (EASI) score of 12 or higher at screening (≥16 at baseline) and inadequate response to topical treatments from 91 study centres, including hospitals, clinics, and academic institutions, in Canada, Czech Republic, Germany, Hungary, Japan, Poland, and the USA. Patients were randomly assigned (1:1:1:1:1:1), stratified by severity (moderate or severe, as assessed by Investigator's Global Assessment) and region (Japan vs rest of world) to receive subcutaneous dupilumab: 300 mg once a week, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, 100 mg every 4 weeks, or placebo once a week for 16 weeks. We used a central randomisation scheme, provided by an interactive voice response system. Drug kits were coded, providing masking to treatment assignment, and allocation was concealed. Patients on treatment every 2 weeks and every 4 weeks received volume-matched placebo every week when dupilumab was not given to ensure double blinding. The primary outcome was efficacy of dupilumab dose regimens based on EASI score least-squares mean percentage change (SE) from baseline to week 16. Analyses included all randomly assigned patients who received one or more doses of study drug. This trial is registered with ClinicalTrials.gov, number NCT01859988. Findings Between May 15, 2013, and Jan 27, 2014, 452 patients were assessed for eligibility, and 380 patients were randomly assigned. 379 patients received one or more doses of study drug (300 mg once a week [n=63], 300 mg every 2 weeks [n=64], 200 mg every 2 weeks [n=61], 300 mg every 4 weeks [n=65], 100 mg every 4 weeks [n=65]; placebo [n=61]). EASI score improvements favoured all dupilumab regimens versus placebo (p<0·0001): 300 mg once a week (-74% [SE 5·16]), 300 mg every 2 weeks (-68% [5·12]), 200 mg every 2 weeks (-65% [5·19]), 300 mg every 4 weeks (-64% [4·94]), 100 mg every 4 weeks (-45% [4·99]); placebo (-18% [5·20]). 258 (81%) of 318 patients given dupilumab and 49 (80%) of 61 patients given placebo reported treatment-emergent adverse events; nasopharyngitis was the most frequent (28% and 26%, respectively). Interpretation Dupilumab improved clinical responses in adults with moderate-to-severe atopic dermatitis in a dose-dependent manner, without significant safety concerns. Our findings show that IL-4 and IL-13 are key drivers of atopic dermatitis. Funding Sanofi and Regeneron Pharmaceuticals.

Thayer, R. E., & Feldstein Ewing, S. W. (2015). *Adolescent psychotherapy for addiction medicine: From brain development to neurocognitive treatment mechanisms* Elsevier.

Effectively treating addiction is a challenge among any population, and treatment for adolescents may be particularly challenging in the context of ongoing neurodevelopment, which may alter the brain's initial response to substances as well as its response to treatment. One way to improve treatment outcomes for youth is to use a translational perspective that explicitly connects cognitive and neurodevelopmental fields with the field of behavioral therapies. This integrative approach is a potential first step to inform the correspondence between the neurocognitive and behavioral fields in youth addiction. This chapter seeks to provide context for neurocognitive treatment studies by first discussing recent structural and functional neuroimaging studies showing associations with substance use or behavioral addictions. Several regions of interest are then proposed that appear to also be associated with addiction treatment across multiple studies, namely, the accumbens/striatum, precuneus, insula, anterior cingulate cortex, and dorsolateral prefrontal cortex. This research suggests that reward, self-reflective, and executive control areas might be especially relevant in youth behavioral treatment response, and preliminary evidence suggests that existing treatments may encourage neurocognitive changes in these areas. © 2015 Elsevier B.V.

Tian, Q., Smart, J. L., Clement, J. H., Wang, Y., Derkatch, A., Schubert, H., et al. (2015). RHEB1 expression in embryonic and postnatal mouse. *Histochemistry and Cell Biology,* , 1-12.

Ras homolog enriched in brain (RHEB1) is a member within the superfamily of GTP-binding proteins encoded by the RAS oncogenes. RHEB1 is located at the crossroad of several important pathways including the insulin-signaling pathways and thus plays an important role in different physiological processes. To understand better the physiological relevance of RHEB1 protein, the expression pattern of RHEB1 was analyzed in both embryonic (at E3.5–E16.5) and adult (1-month old) mice. RHEB1 immunostaining and X-gal staining were used for wild-type and Rheb1 gene trap mutant mice, respectively. These independent methods revealed similar RHEB1 expression patterns during both embryonic and postnatal developments. Ubiquitous uniform RHEB1/β-gal and/or RHEB1 expression was seen in preimplantation embryos at E3.5 and postimplantation embryos up to E12.5. Between stages E13.5 and E16.5, RHEB1 expression

levels became complex: In particular, strong expression was identified in neural tissues, including the neuroepithelial layer of the mesencephalon, telencephalon, and neural tube of CNS and dorsal root ganglia. In addition, strong expression was seen in certain peripheral tissues including heart, intestine, muscle, and urinary bladder. Postnatal mice have broad spatial RHEB1 expression in different regions of the cerebral cortex, subcortical regions (including hippocampus), olfactory bulb, medulla oblongata, and cerebellum (particularly in Purkinje cells). Significant RHEB1 expression was also viewed in internal organs including the heart, intestine, urinary bladder, and muscle. Moreover, adult animals have complex tissue- and organ-specific RHEB1 expression patterns with different intensities observed throughout postnatal development. Its expression level is in general comparable in CNS and other organs of mouse. Thus, the expression pattern of RHEB1 suggests that it likely plays a ubiquitous role in the development of the early embryo with more tissue-specific roles in later development.

Trepte, C. J., Phillips, C. R., Sola, J., Adler, A., Haas, S. A., Rapin, M., et al. (2016). Electrical impedance tomography (EIT) for quantification of pulmonary edema in acute lung injury. *Critical Care (London, England), 20*(1), 18-015-1173-5.

BACKGROUND: Assessment of pulmonary edema is a key factor in monitoring and guidance of therapy in critically ill patients. To date, methods available at the bedside for estimating the physiologic correlate of pulmonary edema, extravascular lung water, often are unreliable or require invasive measurements. The aim of the present study was to develop a novel approach to reliably assess extravascular lung water by making use of the functional imaging capabilities of electrical impedance tomography. METHODS: Thirty domestic pigs were anesthetized and randomized to three different groups. Group 1 was a sham group with no lung injury. Group 2 had acute lung injury induced by saline lavage. Group 3 had vascular lung injury induced by intravenous injection of oleic acid. A novel, noninvasive technique using changes in thoracic electrical impedance with lateral body rotation was used to measure a new metric, the lung water ratioEIT, which reflects total extravascular lung water. The lung water ratioEIT was compared with postmortem gravimetric lung water analysis and transcardiopulmonary thermodilution measurements. RESULTS: A significant correlation was found between extravascular lung water as measured by postmortem gravimetric analysis and electrical impedance tomography (r =

0.80; $p < 0.05$). Significant changes after lung injury were found in groups 2 and 3 in extravascular lung water derived from transcardiopulmonary thermodilution as well as in measurements derived by lung water ratioEIT. CONCLUSIONS: Extravascular lung water could be determined noninvasively by assessing characteristic changes observed on electrical impedance tomograms during lateral body rotation. The novel lung water ratioEIT holds promise to become a noninvasive bedside measure of pulmonary edema.

Troxell, M. L., & Lanciault, C. (2016). Practical applications in immunohistochemistry: Evaluation of rejection and infection in organ transplantation. *Archives of Pathology & Laboratory Medicine,* Context .- Immunohistochemical analysis of tissue biopsy specimens is a crucial tool in diagnosis of both rejection and infection in patients with solid organ transplants. In the past 15 years, the concept of antibody-mediated rejection has been refined, and diagnostic criteria have been codified in renal, heart, pancreas, and lung allografts (with studies ongoing in liver, small intestine, and composite grafts), all of which include immunoanalysis for the complement split product C4d. Objectives .- To review the general concepts of C4d biology and immunoanalysis, followed by organ-allograft-specific data, and interpretative nuances for kidney, pancreas, and heart, with discussion of early literature for lung and liver biopsies. Additionally, practical applications and limitations of immunostains for infectious organisms (Polyomavirus, Adenoviridae (adenovirus), and the herpes virus family, including Herpes simplex virus, Cytomegalovirus, Human herpes virus 8, and Epstein-Barr virus) are reviewed in the context of transplant recipients. Data Sources .- Our experience and published primary and review literature. Conclusions .- Immunohistochemistry continues to have an important role in transplant pathology, most notably C4d staining in assessment of antibody-mediated rejection and assessment of viral pathogens in tissue. In all facets of transplant pathology, correlation of morphology with special studies and clinical data is critical, as is close communication with the transplant team.

Umstattd Meyer, M. R., Perry, C. K., Sumrall, J. C., Patterson, M. S., Walsh, S. M., Clendennen, S. C., et al. (2016). Physical activity-related policy and environmental strategies to prevent obesity in rural communities: A systematic review of the literature, 2002-2013. *Preventing Chronic Disease,*

13, E03.

INTRODUCTION: Health disparities exist between rural and urban residents; in particular, rural residents have higher rates of chronic diseases and obesity. Evidence supports the effectiveness of policy and environmental strategies to prevent obesity and promote health equity. In 2009, the Centers for Disease Control and Prevention recommended 24 policy and environmental strategies for use by local communities: the Common Community Measures for Obesity Prevention (COCOMO); 12 strategies focus on physical activity. This review was conducted to synthesize evidence on the implementation, relevance, and effectiveness of physical activity-related policy and environmental strategies for obesity prevention in rural communities. METHODS: A literature search was conducted in PubMed, PsycINFO, Web of Science, CINHAL, and PAIS databases for articles published from 2002 through May 2013 that reported findings from physical activity-related policy or environmental interventions conducted in the United States or Canada. Each article was extracted independently by 2 researchers. RESULTS: Of 2,002 articles, 30 articles representing 26 distinct studies met inclusion criteria. Schools were the most common setting (n = 18 studies). COCOMO strategies were applied in rural communities in 22 studies; the 2 most common COCOMO strategies were "enhance infrastructure supporting walking" (n = 11) and "increase opportunities for extracurricular physical activity" (n = 9). Most studies (n = 21) applied at least one of 8 non-COCOMO strategies; the most common was increasing physical activity opportunities at school outside of physical education (n = 8). Only 14 studies measured or reported physical activity outcomes (10 studies solely used self-report); 10 reported positive changes. CONCLUSION: Seven of the 12 COCOMO physical activity-related strategies were successfully implemented in 2 or more studies, suggesting that these 7 strategies are relevant in rural communities and the other 5 might be less applicable in rural communities. Further research using robust study designs and measurement is needed to better ascertain implementation success and effectiveness of COCOMO and non-COCOMO strategies in rural communities.

Undurraga Perl, V. J., Leroux, B., Cook, M. R., Watson, J., Fair, K., Martin, D. T., et al. (2016). Damage control resuscitation and emergency laparotomy: Findings from the PROPPR study. *The Journal of Trauma and Acute Care Surgery,*

BACKGROUND: The Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial has demonstrated that damage control resuscitation, a massive transfusion strategy targeting a balanced delivery of plasma-platelet-RBC in a ratio of 1:1:1, results in improved survival at 3 hours and a reduction in deaths due to exsanguination in the first 24 hours compared to a 1:1:2 ratio. In light of these findings, we hypothesized that patients receiving 1:1:1 ratio would have improved survival after emergency laparotomy. METHODS: Severely injured patients predicted to receive a massive transfusion admitted to 12 level I North American trauma centers were randomized to 1:1:1 versus 1:1:2 as described in the PROPPR trial. From these patients, the subset that underwent an emergency laparotomy, defined previously in the literature as laparotomy within 90 minutes of arrival, were identified. We compared rates and timing of emergency laparotomy as well as post-surgical survival at 24-hours and 30-days. RESULTS: Of the 680 enrolled patients, 613 underwent a surgical procedure, 397 underwent a laparotomy, and 346 underwent an emergency laparotomy. The percentages of patients undergoing emergency laparotomy were 51.5% (174/338) and 50.3% (172/342) for 1:1:1 and 1:1:2, respectively (p=0.20). Median time to laparotomy was 28 minutes in both treatment groups. Among patients undergoing an emergency laparotomy, the proportions of patients surviving to 24 hours and 30 days were similar between treatment arms, 24-hour survival was 86.8% (151/174) for 1:1:1 and 83.1% (143/172) for 1:1:2 (p=0.29), and 30-day 79.3% (138/174) for 1:1:1 and 75.0% (129/172) for 1:1:2 (p=0.30). CONCLUSIONS: We found no evidence that resuscitation strategy affects whether a patient requires an emergency laparotomy, time to laparotomy, or subsequent survival. LEVEL OF EVIDENCE: Level IV, therapeutic study.

Ventres, W. B. (2016). Building power between polarities. *Qualitative Health Research, 26*(3), 345-350.

In this article, I introduce the concept of the space-in-between. This space-in-between is born of the realization that, between the expression of any two polarities (across dimensions such as emotion, thought, geography, and ideology), there exists a philosophical construct useful for framing thinking about practice, research, and managerial relationships in the health professions. Out of this construct emerge practical considerations useful for structuring the conduct of meaningful interpersonal and intercultural interactions. I describe how the idea of a space-in-

between developed out of my medical practice, grew as a result of my experiences in international environments. and has found fulfillment in my ongoing work. I explore the application of a space-in-between in public health, medical anthropology, medical ethics, and global health. I review how, as a result of incorporating this space in their daily work, clinicians, educators, researchers, and managers can grow as leaders by sharing the presence that arises from the space-in-between them and the people in the communities they serve. © The Author(s) 2015.

Ventres, W. B. (2016). Healing. *Annals of Family Medicine, 14*(1), 76-78.

My personal ethos of healing is an expression of the belief that I can and do act to heal patients while I attend to the traditional goals of medicine. The 7 supporting principles that inform my ethos are dignity, authenticity, integrity, transparency, solidarity, generosity, and resiliency. I invite others, including medical students, residents, and practicing physicians, to reflect and discover their own ethos of healing and the principles that guide their professional growth. A short digital documentary accompanies this essay for use as a reflective prompt to encourage personal and professional development.

Vinukonda, G., Dohare, P., Arshad, A., Zia, M. T., Panda, S., Korumilli, R., et al. (2016). Hyaluronidase and hyaluronan oligosaccharides promote neurological recovery after intraventricular hemorrhage. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 36*(3), 872-889.

Intraventricular hemorrhage (IVH) in premature infants results in inflammation, arrested oligodendrocyte progenitor cell (OPC) maturation, and reduced myelination of the white matter. Hyaluronan (HA) inhibits OPC maturation and complexes with the heavy chain (HC) of glycoprotein inter-alpha-inhibitor to form pathological HA (HC-HA complex), which exacerbates inflammation. Therefore, we hypothesized that IVH would result in accumulation of HA, and that either degradation of HA by hyaluronidase treatment or elimination of HCs from pathological HA by HA oligosaccharide administration would restore OPC maturation, myelination, and neurological function in survivors with IVH. To test these hypotheses, we used the preterm rabbit model of glycerol-induced IVH and analyzed autopsy samples from premature infants. We found

that total HA levels were comparable in both preterm rabbit pups and human infants with and without IVH, but HA receptors-CD44, TLR2, TLR4-were elevated in the forebrain of both humans and rabbits with IVH. Hyaluronidase treatment of rabbits with IVH reduced CD44 and TLR4 expression, proinflammatory cytokine levels, and microglia infiltration. It also promoted OPC maturation, myelination, and neurological recovery. HC-HA and tumor necrosis factor-stimulated gene-6 were elevated in newborns with IVH; and depletion of HC-HA levels by HA oligosaccharide treatment reduced inflammation and enhanced myelination and neurological recovery in rabbits with IVH. Hence, hyaluronidase or HA oligosaccharide treatment represses inflammation, promotes OPC maturation, and restores myelination and neurological function in rabbits with IVH. These therapeutic strategies might improve the neurological outcome of premature infants with IVH. SIGNIFICANCE STATEMENT: Approximately 12,000 premature infants develop IVH every year in the United States, and a large number of survivors with IVH develop cerebral palsy and cognitive deficits. The onset of IVH induces inflammation of the periventricular white matter, which results in arrested maturation of OPCs and myelination failure. HA is a major component of the extracellular matrix of the brain, which regulates inflammation through CD44 and TLR2/4 receptors. Here, we show two mechanism-based strategies that effectively enhanced myelination and neurological recovery in preterm rabbit model of IVH. First, degrading HA by hyaluronidase treatment reduced CD44 and TLR4 expression, proinflammatory cytokines, and microglial infiltration, as well as promoted oligodendrocyte maturation and myelination. Second, intraventricular injection of HA oligosaccharide reduced inflammation and enhanced myelination, conceivably by depleting HC-HA levels.

Virgini, V. S., Rodondi, N., Cawthon, P. M., Harrison, S. L., Hoffman, A. R., Orwoll, E. S., et al. (2015). Subclinical thyroid dysfunction and frailty among older men. *Journal of Clinical Endocrinology and Metabolism, 100*(12), 4524-4532.

Context: Both subclinical thyroid dysfunction and frailty are common among older individuals, but data on the relationship between these 2 conditions are conflicting. Objective: The purpose of this study was to assess the cross-sectional and prospective associations between subclinical thyroid dysfunction and frailty and the 5 frailty subdomains (sarcopenia, weakness, slowness, exhaustion, and low activity). Setting and Design: The Osteoporotic Fractures in Men Study is a

prospective cohort study. Participants: Men older than 65 years (n = 1455) were classified into 3 groups of thyroid status: subclinical hyperthyroidism (n = 26, 1.8%), subclinical hypothyroidism (n = 102, 7.0%), and euthyroidism (n = 1327, 91.2%). MainOutcomeMeasures: Frailty was defined using a slightly modified Cardiovascular Health Study Index: men with 3 or more criteria were considered frail, men with 1 to 2 criteria were considered intermediately frail, and men with no criteria were considered robust. We assessed the crosssectional relationship between baseline thyroid function and the 3 categories of frailty status (robust/intermediate/frail) as well as the prospective association between baseline thyroid function and subsequent frailty status and mortality after a 5-year follow-up. Results: At baseline, compared with euthyroid participants,menwith subclinical hyperthyroidism had an increased likelihood of greater frailty status (adjusted odds ratio, 2.48; 95% confidence interval, 1.15-5.34), particularly among men aged <74 years at baseline (odds ratio for frailty, 3.63; 95% confidence interval, 1.21-10.88). After 5 years of follow-up, baseline subclinical hypothyroidism and hyperthyroidism were not consistently associated with overall frailty status or frailty components. Conclusion: Among community-dwelling older men, subclinical hyperthyroidism, but not subclinical hypothyroidism, is associated with increased odds of prevalent but not incident frailty.

Vogel, J. A., Newgard, C. D., Holmes, J. F., Diercks, D. B., Arens, A. M., Boatright, D. H., et al. (2016). Validation of the denver emergency department trauma organ failure score to predict post-injury multiple organ failure presented, in part, at the research forum of the american college of emergency physicians' scientific assembly, seattle, WA, october 2013. *Journal of the American College of Surgeons, 222*(1), 73-82.

Background Early recognition of trauma patients at risk for multiple organ failure (MOF) is important to reduce the morbidity and mortality associated with MOF. The objective of the study was to externally validate the Denver Emergency Department (ED) Trauma Organ Failure (TOF) Score, a 6-item instrument that includes age, intubation, hematocrit, systolic blood pressure, blood urea nitrogen, and white blood cell count, which was designed to predict the development of MOF within 7 days of hospitalization. Study Design We performed a prospective multicenter study of adult trauma patients between November, 2011 and March, 2013. The primary outcome

was development of MOF within 7 days of hospitalization, assessed using the Sequential Organ Failure Assessment Score. Hierarchical logistic regression analysis was performed to determine associations between the Denver ED TOF Score and MOF. Discrimination was assessed and quantified using a receiver operating characteristics (ROC) curve. The predictive accuracy of the Denver ED TOF score was compared with attending emergency physician estimation of the likelihood of MOF. Results We included 2,072 patients with a median age of 46 years (interquartile range [IQR] 30 to 61 years); 68% were male. The median Injury Severity Score was 9 (IQR 5 to 17), and 88% of patients had blunt mechanism injury. Among participants, 1,024 patients (49%) were admitted to the ICU, and 77 (4%) died. Multiple organ failure occurred in 120 (6%; 95% CI 5% to 7%) patients and of these, 37 (31%; 95% CI 23% to 40%) died. The area under the ROC curve for the Denver ED TOF Score prediction of MOF was 0.89 (95% CI 0.86 to 0.91) and for physician estimation of the likelihood of MOF was 0.78 (95% CI 0.73 to 0.83). Conclusions The Denver ED TOF Score predicts development of MOF within 7 days of hospitalization. Its predictive accuracy outperformed attending emergency physician estimation of the risk of MOF. © 2016 American College of Surgeons.

Volden, J., Duku, E., Shepherd, C., Ba, Georgiades, S., Bennett, T., et al. (2015). Service utilization in a sample of preschool children with autism spectrum disorder: A canadian snapshot. *Paediatrics & Child Health, 20*(8), e43-7.

OBJECTIVE: To describe services received by preschool children diagnosed with autism spectrum disorder (ASD) during the five-year period following their diagnosis. METHOD: An inception cohort of preschoolers diagnosed with ASD from Halifax (Nova Scotia), Montreal (Quebec), Hamilton (Ontario), Edmonton (Alberta) and Vancouver (British Columbia) were invited to participate. Parents/caregivers (n=414) described the services provided to their children at four time points: baseline (T1; within four months of diagnosis; mean age three years); six months later (T2); 12 months later (T3); and at school entry (T4). Data were first coded into 11 service types and subsequently combined into four broader categories (no services, behavioural, developmental and general) for analysis. RESULTS: More than 80% of children at T1, and almost 95% at T4 received some type of service, with a significant number receiving >1 type of service at each assessment point. At T1, the most common service was developmental (eg, speech-

language therapy). Subsequently, the most common services were a combination of behavioural and developmental (eg, intensive therapy based on applied behaviour analysis and speech-language therapy). Service provision varied across provinces and over time. DISCUSSION: Although most preschool children with ASD residing in urban centres were able to access specialized services shortly after diagnosis, marked variation in services across provinces remains a concern.; Publisher: Abstract available from the publisher.

Wahbeh, H., Goodrich, E., Goy, E., & Oken, B. S. (2016). Mechanistic pathways of mindfulness meditation in combat veterans with posttraumatic stress disorder. *Journal of Clinical Psychology,* OBJECTIVE: This study's objective was to evaluate the effect of two common components of meditation (mindfulness and slow breathing) on potential mechanistic pathways. METHODS: A total of 102 combat veterans with posttraumatic stress disorder (PTSD) were randomized to (a) the body scan mindfulness meditation (MM), (b) slow breathing (SB) with a biofeedback device, (c) mindful awareness of the breath with an intention to slow the breath (MM+SB), or (d) sitting quietly (SQ). Participants had 6 weekly one-on-one sessions with 20 minutes of daily home practice. The mechanistic pathways and measures were as follows: (a) autonomic nervous system (hyperarousal symptoms, heart rate [HR], and heart rate variability [HRV]); (b) frontal cortex activity (attentional network task [ANT] conflict effect and event-related negativity and intrusive thoughts); and (c) hypothalamic-pituitary-adrenal axis (awakening cortisol). PTSD measures were also evaluated. RESULTS: Meditation participants had significant but modest within-group improvement in PTSD and related symptoms, although there were no effects between groups. Perceived impression of PTSD symptom improvement was greater in the meditation arms compared with controls. Resting respiration decreased in the meditation arms compared with SQ. For the mechanistic pathways, (a) subjective hyperarousal symptoms improved within-group (but not between groups) for MM, MM+SB, and SQ, while HR and HRV did not; (b) intrusive thoughts decreased in MM compared with MM+SB and SB, while the ANT measures did not change; and (c) MM had lower awakening cortisol within-group (but not between groups). CONCLUSION: Treatment effects were mostly specific to self-report rather than physiological measures. Continued research is needed to further evaluate mindfulness meditation's mechanism in people with PTSD.

Wang, K., Mateos-Aparicio, P., Honigsperger, C., Raghuram, V., Wu, W. W., Ridder, M. C., et al. (2016). IK1 channels do not contribute to the slow afterhyperpolarization in pyramidal neurons. *Elife, 5*, 10.7554/eLife.11206.

In pyramidal neurons such as hippocampal area CA1 and basolateral amygdala, a slow afterhyperpolarization (sAHP) follows a burst of action potentials, which is a powerful regulator of neuronal excitability. The sAHP amplitude increases with aging and may underlie age related memory decline. The sAHP is due to a Ca(2+)-dependent, voltage-independent K(+) conductance, the molecular identity of which has remained elusive until a recent report suggested the Ca(2+)-activated K(+) channel, IK1 (KCNN4) as the sAHP channel in CA1 pyramidal neurons. The signature pharmacology of IK1, blockade by TRAM-34, was reported for the sAHP and underlying current. We have examined the sAHP and find no evidence that TRAM-34 affects either the current underling the sAHP or excitability of CA1 or basolateral amygdala pyramidal neurons. In addition, CA1 pyramidal neurons from IK1 null mice exhibit a characteristic sAHP current. Our results indicate that IK1 channels do not mediate the sAHP in pyramidal neurons.

Wang, X., Beste, L. A., Maier, M. M., & Zhou, X. H. (2016). Double robust estimator of average causal treatment effect for censored medical cost data. *Statistics in Medicine,*

In observational studies, estimation of average causal treatment effect on a patient's response should adjust for confounders that are associated with both treatment exposure and response. In addition, the response, such as medical cost, may have incomplete follow-up. In this article, a double robust estimator is proposed for average causal treatment effect for right censored medical cost data. The estimator is double robust in the sense that it remains consistent when either the model for the treatment assignment or the regression model for the response is correctly specified. Double robust estimators increase the likelihood the results will represent a valid inference. Asymptotic normality is obtained for the proposed estimator, and an estimator for the asymptotic variance is also derived. Simulation studies show good finite sample performance of the proposed estimator and a real data analysis using the proposed method is provided as illustration. Copyright (c) 2016 John Wiley & Sons, Ltd.

Watanabe, K. H., Mayo, M., Jensen, K. M., Villeneuve, D. L., Ankley, G. T., & Perkins, E. J. (2016). Predicting fecundity of fathead minnows (pimephales promelas) exposed to endocrine-disrupting chemicals using a MATLAB(R)-based model of oocyte growth dynamics. *PloS One, 11*(1), e0146594.

Fish spawning is often used as an integrated measure of reproductive toxicity, and an indicator of aquatic ecosystem health in the context of forecasting potential population-level effects considered important for ecological risk assessment. Consequently, there is a need for flexible, widely-applicable, biologically-based models that can predict changes in fecundity in response to chemical exposures, based on readily measured biochemical endpoints, such as plasma vitellogenin (VTG) concentrations, as input parameters. Herein we describe a MATLAB(R) version of an oocyte growth dynamics model for fathead minnows (Pimephales promelas) with a graphical user interface based upon a previously published model developed with MCSim software and evaluated with data from fathead minnows exposed to an androgenic chemical, 17beta-trenbolone. We extended the evaluation of our new model to include six chemicals that inhibit enzymes involved in steroid biosynthesis: fadrozole, ketoconazole, propiconazole, prochloraz, fenarimol, and trilostane. In addition, for unexposed fathead minnows from group spawning design studies, and those exposed to the six chemicals, we evaluated whether the model is capable of predicting the average number of eggs per spawn and the average number of spawns per female, which was not evaluated previously. The new model is significantly improved in terms of ease of use, platform independence, and utility for providing output in a format that can be used as input into a population dynamics model. Model-predicted minimum and maximum cumulative fecundity over time encompassed the observed data for fadrozole and most propiconazole, prochloraz, fenarimol and trilostane treatments, but did not consistently replicate results from ketoconazole treatments. For average fecundity (eggs*female-1*day-1), eggs per spawn, and the number of spawns per female, the range of model-predicted values generally encompassed the experimentally observed values. Overall, we found that the model predicts reproduction metrics robustly and its predictions capture the variability in the experimentally observed data.

Webb, B. C., Whittle, T., & Schwarz, E. (2015). Provision of dental care in aged care facilities NSW australia- part 2 as perceived by the carers (care providers). *Gerodontology, 32*(4), 254-259. Objectives To investigate carers' perception of the provision of dental care in aged care facilities (ACFs) New South Wales (NSW), Australia. Background Carers are responsible for 'hands-on, day-to-day' care of residents, including dental care, yet there were no specific figures available concerning their role in NSW ACFs. Materials and Methods Questionnaires were mailed to 406 NSW directors of nursing (DONs) requesting completion by a carer who was proficient in English and without the influence of the DON. The 23-item questionnaire was presented in 4 sections, and the data qualitatively analysed. Results 211 questionnaires were completed and returned, giving a response rate of 52%. Carers were mostly female (91.9%) in the 40-50 and >50 age groups. Oral health training had been received by 66.7% of carers, and although 73.2% thought that their training was adequate, carers in general requested further training. Long waiting periods for government dental services (69.4%) and resident unable to communicate oral health problems (69.2%) were seen as the most frequent barriers to dental care. Almost all carers reported the availability of electric tooth brushes, fluoride gel, disclosing tablets/gel, interdental brushes and the use of a foam mouth prop, while few reported the use of other dental care products. Conclusion As carers provided almost all of oral health care for residents, emphasis should be placed on training in geriatric dental care techniques and use of dental products. © 2013 John Wiley & Sons A/S and The Gerodontology Society. Published by John Wiley & Sons Ltd.

Weisschuh, N., Mayer, A. K., Strom, T. M., Kohl, S., Glockle, N., Schubach, M., et al. (2016). Mutation detection in patients with retinal dystrophies using targeted next generation sequencing. *PloS One, 11*(1), e0145951.

Retinal dystrophies (RD) constitute a group of blinding diseases that are characterized by clinical variability and pronounced genetic heterogeneity. The different nonsyndromic and syndromic forms of RD can be attributed to mutations in more than 200 genes. Consequently, next generation sequencing (NGS) technologies are among the most promising approaches to identify mutations in RD. We screened a large cohort of patients comprising 89 independent cases and families with various subforms of RD applying different NGS platforms. While mutation screening in 50 cases was performed using a RD gene capture panel, 47 cases were analyzed using whole

exome sequencing. One family was analyzed using whole genome sequencing. A detection rate of 61% was achieved including mutations in 34 known and two novel RD genes. A total of 69 distinct mutations were identified, including 39 novel mutations. Notably, genetic findings in several families were not consistent with the initial clinical diagnosis. Clinical reassessment resulted in refinement of the clinical diagnosis in some of these families and confirmed the broad clinical spectrum associated with mutations in RD genes.

Weleber, R. G. (2016). Dysregulation of retinal transcription factor PRDM13 and north carolina macular dystrophy. *Ophthalmology, 123*(1), 2-4.

Wilhelm, C. J., & Guizzetti, M. (2016). Fetal alcohol spectrum disorders: An overview from the glia perspective. *Frontiers in Integrative Neuroscience, 9*, 65.

Alcohol consumption during pregnancy can produce a variety of central nervous system (CNS) abnormalities in the offspring resulting in a broad spectrum of cognitive and behavioral impairments that constitute the most severe and long-lasting effects observed in fetal alcohol spectrum disorders (FASD). Alcohol-induced abnormalities in glial cells have been suspected of contributing to the adverse effects of alcohol on the developing brain for several years, although much research still needs to be done to causally link the effects of alcohol on specific brain structures and behavior to alterations in glial cell development and function. Damage to radial glia due to prenatal alcohol exposure may underlie observations of abnormal neuronal and glial migration in humans with Fetal Alcohol Syndrome (FAS), as well as primate and rodent models of FAS. A reduction in cell number and altered development has been reported for several glial cell types in animal models of FAS. In utero alcohol exposure can cause microencephaly when alcohol exposure occurs during the brain growth spurt a period characterized by rapid astrocyte proliferation and maturation; since astrocytes are the most abundant cells in the brain, microenchephaly may be caused by reduced astrocyte proliferation or survival, as observed in in vitro and in vivo studies. Delayed oligodendrocyte development and increased oligodendrocyte precursor apoptosis has also been reported in experimental models of FASD, which may be linked to altered myelination/white matter integrity found in FASD children. Children with FAS exhibit hypoplasia of the corpus callosum and anterior commissure, two areas requiring guidance from

glial cells and proper maturation of oligodendrocytes. Finally, developmental alcohol exposure disrupts microglial function and induces microglial apoptosis; given the role of microglia in synaptic pruning during brain development, the effects of alcohol on microglia may be involved in the abnormal brain plasticity reported in FASD. The consequences of prenatal alcohol exposure on glial cells, including radial glia and other transient glial structures present in the developing brain, astrocytes, oligodendrocytes and their precursors, and microglia contributes to abnormal neuronal development, reduced neuron survival and disrupted brain architecture and connectivity. This review highlights the CNS structural abnormalities caused by in utero alcohol exposure and outlines which abnormalities are likely mediated by alcohol effects on glial cell development and function.

Willenbring, B. D., Lerner, E. B., Brasel, K., Cushman, J. T., Guse, C. E., Shah, M. N., et al. (2016). Evaluation of a consensus-based criterion standard definition of trauma center need for use in field triage research. *Prehospital Emergency Care, 20*(1), 1-5.

Research on field triage of injured patients is limited by the lack of a widely used criterion standard for defining trauma center need. Injury Severity Score (ISS) >15 has been a commonly used outcome measure in research for determining trauma center need that has never been validated. A multidisciplinary team recently published a consensus-based criterion standard definition of trauma center need, but this measure has not yet been validated. The objective was to determine if the consensus-based criterion standard can be obtained by medical record review and compare patients identified as needing a trauma center by the consensus-based criterion standard vs. ISS >15. A subanalysis of data collected during a 2-year prospective cohort study of 4,528 adult trauma patients transported by EMS to a single trauma center was conducted. These data included ICD-9-CM codes, treatment times, and other patient care data. Presence of the consensus-based criterion standard was determined for each patient. ISS was calculated based on ICD-9-CM codes assigned for billing. The consensus-based criterion standard could be applied to 4,471 (98.7%) cases. ISS could be determined for 4,506 (99.5%) cases. Based on an ISS >15, 8.9% of cases were identified as needing a trauma center. Of those, only 48.2% met the consensus-based criterion standard. Almost all patients that did not meet the consensus-based criterion standard, but had an ISS >15 were diagnosed with chest (rib fractures (100/205

cases)/pneumothorax (57/205 cases), closed head (without surgical intervention 88/205 cases), vertebral (without spinal cord injury 45/205 cases), and/or extremity injuries (39/205 cases). There were 4,053 cases with an ISS <15. 5.0% of those with an ISS <15 met the consensus-based criterion standard with the majority requiring surgery (139/203 cases) or a blood transfusion (60/203 cases). The kappa coefficient of agreement for ISS and the consensus-based criterion standard was 0.43. We determined that the consensus-based criterion standard could be identified through a medical record review. Use of the consensus-based criterion standard for field triage research will more accurately identify injured patients who need the resources of a trauma center when compared to ISS. © 2016 National Association of EMS Physicians.

Winham, S. J., Pirie, A., Chen, Y. A., Larson, M. C., Fogarty, Z. C., Earp, M. A., et al. (2016). Investigation of exomic variants associated with overall survival in ovarian cancer. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology,*

BACKGROUND: While numerous susceptibility loci for epithelial ovarian cancer (EOC) have been identified, few associations have been reported with overall survival. In the absence of common prognostic genetic markers, we hypothesize that rare coding variants may be associated with overall EOC survival and assessed their contribution in two exome-based genotyping projects of the Ovarian Cancer Association Consortium (OCAC). METHODS: The primary patient set (Set 1) included 14 independent EOC studies (4293 patients) and 227,892 variants, and a secondary patient set (Set 2) included six additional EOC studies (1744 patients) and 114,620 variants. Because power to detect rare variants individually is reduced, gene-level tests were conducted. Sets were analyzed separately at individual variants and by gene, and then combined with meta-analyses (73,203 variants and 13,163 genes overlapped). RESULTS: No individual variant reached genome-wide statistical significance. A SNP previously implicated to be associated with EOC risk and, to a lesser extent, survival, rs8170, showed the strongest evidence of association with survival and similar effect size estimates across sets (Pmeta=1.1E-6, HRSet1=1.17, HRSet2=1.14). Rare variants in ATG2B, an autophagy gene important for apoptosis, were significantly associated with survival after multiple testing correction (Pmeta=1.1E-6; Pcorrected=0.01). CONCLUSIONS: Common variant rs8170 and rare variants in ATG2B may be

associated with EOC overall survival, although further study is needed. IMPACT: This study represents the first exome-wide association study of EOC survival to include rare variant analyses, and suggests that complementary single variant and gene-level analyses in large studies are needed to identify rare variants that warrant follow-up study.

Winn, S. R., Scherer, T., Thöny, B., & Harding, C. O. (2016). High dose sapropterin dihydrochloride therapy improves monoamine neurotransmitter turnover in murine phenylketonuria (PKU). *Molecular Genetics and Metabolism, 117*(1), 5-11.

Central nervous system (CNS) deficiencies of the monoamine neurotransmitters, dopamine and serotonin, have been implicated in the pathophysiology of neuropsychiatric dysfunction in phenylketonuria (PKU). Increased brain phenylalanine concentration likely competitively inhibits the activities of tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH), the rate limiting steps in dopamine and serotonin synthesis respectively. Tetrahydrobiopterin (BH4) is a required cofactor for TH and TPH activity. Our hypothesis was that treatment of hyperphenylalaninemic Pahenu2/enu2 mice, a model of human PKU, with sapropterin dihydrochloride, a synthetic form of BH4, would stimulate TH and TPH activities leading to improved dopamine and serotonin synthesis despite persistently elevated brain phenylalanine. Sapropterin (20, 40, or 100mg/kg body weight in 1% ascorbic acid) was administered daily for 4days by oral gavage to Pahenu2/enu2 mice followed by measurement of brain biopterin, phenylalanine, tyrosine, tryptophan and monoamine neurotransmitter content. A significant increase in brain biopterin content was detected only in mice that had received the highest sapropterin dose, 100mg/kg. Blood and brain phenylalanine concentrations were unchanged by sapropterin therapy. Sapropterin therapy also did not alter the absolute amounts of dopamine and serotonin in brain but was associated with increased homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), dopamine and serotonin metabolites respectively, in both wild type and Pahenu2/enu2 mice. Oral sapropterin therapy likely does not directly affect central nervous system monoamine synthesis in either wild type or hyperphenylalaninemic mice but may stimulate synaptic neurotransmitter release and subsequent metabolism.

Winters-Stone, K. M., Lyons, K. S., Dobek, J., Dieckmann, N. F., Bennett, J. A., Nail, L., et al. (2015). Benefits of partnered strength training for prostate cancer survivors and spouses: Results from a randomized controlled trial of the exercising together project. *Journal of Cancer Survivorship,* , 1-12.

Background: Prostate cancer can negatively impact quality of life of the patient and his spouse caregiver, but interventions rarely target the health of both partners simultaneously. We tested the feasibility and preliminary efficacy of a partnered strength training program on the physical and mental health of prostate cancer survivors (PCS) and spouse caregivers. Methods: Sixty-four couples were randomly assigned to 6 months of partnered strength training (Exercising Together, N = 32) or usual care (UC, N = 32). Objective measures included body composition (lean, fat and trunk fat mass (kg), and % body fat) by DXA, upper and lower body muscle strength by 1-repetition maximum, and physical function by the physical performance battery (PPB). Self-reported measures included the physical and mental health summary scales and physical function and fatigue subscales of the SF-36 and physical activity with the CHAMPS questionnaire. Results: Couple retention rates were 100 % for Exercising Together and 84 % for UC. Median attendance of couples to Exercising Together sessions was 75 %. Men in Exercising Together became stronger in the upper body ($p < 0.01$) and more physically active ($p < 0.01$) than UC. Women in Exercising Together increased muscle mass ($p = 0.05$) and improved upper ($p < 0.01$) and lower body ($p < 0.01$) strength and PPB scores ($p = 0.01$) more than UC. Conclusions: Exercising Together is a novel couples-based approach to exercise that was feasible and improved several health outcomes for both PCS and their spouses. Implications for cancer survivors: A couples-based approach should be considered in cancer survivorship programs so that outcomes can mutually benefit both partners. Trial registration: ClinicalTrials.gov NCT00954044

Wolf, G. M. (2016). Letter-sound reading: Teaching preschool children print-to-sound processing. *Early Childhood Education Journal, 44*(1), 11-19.

This intervention study investigated the growth of letter sound reading and growth of consonant–vowel–consonant (CVC) word decoding abilities for a representative sample of 41 US children in preschool settings. Specifically, the study evaluated the effectiveness of a 3-step letter-sound

teaching intervention in teaching preschool children to decode, or read, single letters. The study compared a control group, which received the preschool's standard letter-sound instruction, to an intervention group which received a 3-step letter-sound instruction intervention. The children's growth in letter-sound reading and CVC word decoding abilities were assessed at baseline and 2, 4, 6 and 8 weeks. When compared to the control group, the growth of letter-sound reading ability was slightly higher for the intervention group. The rate of increase in letter-sound reading was significantly faster for the intervention group. In both groups, too few children learned to decode any CVC words to allow for analysis. Results of this study support the use of the intervention strategy in preschools for teaching children print-to-sound processing. © 2014, Springer Science+Business Media New York.

Wu, H. L., Léon, E. J., Wallace, L. T., Nimiyongskul, F. A., Buechler, M. B., Newman, L. P., et al. (2016). Identification and spontaneous immune targeting of an endogenous retrovirus K envelope protein in the indian rhesus macaque model of human disease. *Retrovirology,* Background: Endogenous retroviruses (ERVs) are remnants of ancient retroviral infections that have invaded the germ line of both humans and non-human primates. Most ERVs are functionally crippled by deletions, mutations, and hypermethylation, leading to the view that they are inert genomic fossils. However, some ERVs can produce mRNA transcripts, functional viral proteins, and even non-infectious virus particles during certain developmental and pathological processes. While there have been reports of ERV-specific immunity associated with ERV activity in humans, adaptive immune responses to ERV-encoded gene products remain poorly defined and have not been investigated in the physiologically relevant non-human primate model of human disease. Findings: Here, we identified the rhesus macaque equivalent of the biologically active human ERV-K (HML-2), simian ERV-K (SERV-K1), which retains intact open reading frames for both Gag and Env on chromosome 12 in the macaque genome. From macaque cells we isolated a spliced mRNA product encoding SERV-K1 Env, which possesses all the structural features of a canonical, functional retroviral Envelope protein. Furthermore, we identified rare, but robust T cell responses as well as frequent antibody responses targeting SERV-K1 Env in rhesus macaques. Conclusions: These data demonstrate that SERV-K1 retains biological activity sufficient to induce cellular and humoral immune responses in rhesus macaques. As ERV-K is the youngest and most

active ERV family in the human genome, the identification and characterization of the simian orthologue in rhesus macaques provides a highly relevant animal model in which to study the role of ERV-K in developmental and disease states. © 2016 Wu et al.

Xu, C., Zhang, B., Zhu, L., Lin, S., Sun, X., Jiang, Z., et al. (2016). Sequestration of antimonite by zerovalent iron: Using weak magnetic field effects to enhance performance and characterize reaction mechanisms. *Environmental Science & Technology,*

Many oxyanion-forming metals (As, Sb, Se, Tc, etc.) can be removed from water by adsorption and/or redox reactions involving iron oxides, including the oxides associated with zerovalent iron (ZVI). The rate of antimonite (Sb(III) hydrolysis species) removal by ZVI was determined in open, well-mixed batch reactors as a function of experimental factors, including aging of the ZVI, addition of Fe(II), Sb dose, mixing rate, pH, initial concentrations of Sb(III), etc. However, the largest effect observed was the roughly 6-8 fold increase in Sb(III) removal rate due to the application of a weak magnetic field (WMF) during the experiments. The WMF effect on Sb removal arises from stimulated corrosion and delayed passivation of the ZVI, as evidenced by time series correlation analysis of "geochemical" properties (DO, Fetot, Eh, and pH) measured synchronously in each experiment. The removal of Sb under the conditions of this study was mainly due to oxidation of Sb(III) to Sb(V) and adsorption and coprecipitation onto the iron oxides formed from accelerated corrosion of ZVI, as evidenced by Sb K-edge XANES, EXAFS, and XPS. The degree of the WMF enhancement for Sb(III) was found to be similar to the WMF effect reported previously for Sb(V), As(III), As(V), and Se(VI).

Yackel, T. R. (2016). Capsule commentary on lee et al., patient use of email, facebook, and physicians' websites to communicate with physicians: A national online survey of retail pharmacy users. *Journal of General Internal Medicine, 31*(1), 102.

Yan, L., Hicks, M., Winslow, K., Comella, C., Ludlow, C., Jinnah, H. A., et al. (2015). Secured web-based video repository for multicenter studies. *Parkinsonism & Related Disorders, 21*(4), 366-371.

BACKGROUND: We developed a novel secured web-based dystonia video repository for the Dystonia Coalition, part of the Rare Disease Clinical Research network funded by the Office of

Rare Diseases Research and the National Institute of Neurological Disorders and Stroke. A critical component of phenotypic data collection for all projects of the Dystonia Coalition includes a standardized video of each participant. We now describe our method for collecting, serving and securing these videos that is widely applicable to other studies. METHODS: Each recruiting site uploads standardized videos to a centralized secured server for processing to permit website posting. The streaming technology used to view the videos from the website does not allow downloading of video files. With appropriate institutional review board approval and agreement with the hosting institution, users can search and view selected videos on the website using customizable, permissions-based access that maintains security yet facilitates research and quality control. RESULTS: This approach provides a convenient platform for researchers across institutions to evaluate and analyze shared video data. We have applied this methodology for quality control, confirmation of diagnoses, validation of rating scales, and implementation of new research projects. CONCLUSIONS: We believe our system can be a model for similar projects that require access to common video resources.

Yang, E., Kahn, D., & Cook, C. (2015). Acute appendicitis in south africa: A systematic review. *South African Journal of Surgery, 53*(3-4)

Background: Acute appendicitis is one of the most common surgical emergencies in the West. A large body of research is investigating the risk factors for disease and perforation. As South Africa has a social environment, health system structure, and population demography unique from developed nations, the findings may not be generalisable to this setting. A systematic review has not been performed for appendicitis research in South Africa. The objective of this review was to systematically examine the literature on appendicitis in South Africa. Method: Published articles discussing appendicitis in South Africa up to March 2014 were identified using MEDLINE and EBMReviews. Research themes were analysed in the literature. Perforation rates, mortality, negative appendicectomy rates and gender differences were analysed from audits of patients undergoing appendicectomy for acute appendicitis. Results: Ten audits were included in the quantitative analysis. Some were excluded in the subgroup analyses. Negative appendicectomies occurred at a rate of 17% (580/3 354). Women were more likely to have a negative appendicectomy than men (28% vs. 9%, $p < 0.01$). The perforation rate for appendicectomy

patients was 36% (970/2 688), and mortality rate was 1% (36/2 946). Research efforts focused on investigating differential incidence and outcomes between racial groups within the country. Conclusion: Appendicitis trends in South Africa are consistent with those in developing regions. However, there is lack of research from the private sector. Further research is needed to investigate specific factors which delay care, outcomes and cost analyses for laparoscopic surgery, and the system strengthening of surgical services at district hospitals.

Yang, R., Bentley, M., Huang, C. F., & Banker, G. (2016). Analyzing kinesin motor domain translocation in cultured hippocampal neurons. *Methods in Cell Biology, 131*, 217-232. Neuronal microtubules are subject to extensive posttranslational modifications and are bound by MAPs, tip-binding proteins, and other accessory proteins. All of these features, which are difficult to replicate in vitro, are likely to influence the translocation of kinesin motors. Here we describe assays for evaluating the translocation of a population of fluorescently labeled kinesin motor domains, based on their accumulation in regions of the cell enriched in microtubule plus ends. Neurons lend themselves to these experiments because of their microtubule organization. In axons, microtubules are oriented with their plus ends out; dendrites contain a mixed population of microtubules, but those near the tips are also plus end out. The assays involve the expression of constitutively active kinesins that can walk processively, but that lack the autoinhibitory domain in the tail that normally prevents their binding to microtubules until they attach to vesicles. The degree to which such motor domains accumulate at neurite tips serves as a measure of the efficiency of their translocation. Although these assays cannot provide the kind of quantitative kinetic information obtained from in vitro assays, they offer a simple way to examine kinesin translocation in living neurons. They can be used to compare the translocation efficiency of different kinesin motors and to evaluate how mutations or posttranslational modifications within the motor domain influence kinesin translocation. Changes to motor domain accumulation in these assays can also serve as readout for changes in the microtubule cytoskeleton that affect kinesin translocation.

Yao, J., Hinson, H. E., & Simon, J. H. (2014). Delirium and confusion. (pp. 19-33) Cambridge University Press.

Delirium and confusional states are among the most common disorders affecting adults admitted to a hospital. Delirious patients may present dramatically, exhibiting agitated, combative behavior. Or, signs of delirium might be more subtle, remaining undetected by an unsuspecting clinician. The spectrum of delirium poses significant challenges for hospital staff and family alike. Moreover, delirium is also strongly associated with negative outcomes and adds significantly to the cost of healthcare. The recognition of confusion and delirium may, on the surface, seem simple, but the available evidence suggests otherwise [1, 2]. These are not disease diagnoses in their own right, but rather symptoms of an underlying disorder. Delirium and confusional states are clinical syndromes with many potential causes. The greater diagnostic challenge often lies in identifying the underlying disease or disturbances. Obtaining a useful history and examination can be difficult, if not impossible. Since delirium and confusional states can be seen in such a wide range of diseases, no one diagnostic test is reliably informative in their evaluation. Therefore, the clinician must take a systematic approach to the delirious patient. Despite being a daily occurrence in nearly every hospital, our understanding of delirium and confusional states remains limited. The heterogeneous nature of the condition makes studying delirium difficult, which is a barrier to both clinical management and research. Practice guidelines based on expert opinion must still rely heavily on the results of small and/or observational rather than prospective studies [3]. This chapter reviews the current definition of delirium and confusional states, highlighting its key features. A systematic approach is key to identifying the underlying cause or causes of delirium so that the appropriate treatment can then be applied.

Yarborough, B. J., Stumbo, S. P., McCarty, D., Mertens, J., Weisner, C., & Green, C. A. (2016). Methadone, buprenorphine and preferences for opioid agonist treatment: A qualitative analysis. *Drug and Alcohol Dependence,*

BACKGROUND: Patients and clinicians have begun to recognize the advantages and disadvantages of buprenorphine relative to methadone, but factors that influence choices between these two medications remain unclear. For example, we know little about how patients' preferences and previous experiences influence treatment decisions. Understanding these issues may enhance treatment engagement and retention. METHODS: Adults with opioid dependence

(n=283) were recruited from two integrated health systems to participate in interviews focused on prior experiences with treatment for opioid dependence, knowledge of medication options, preferences for treatment, and experiences with treatment for chronic pain in the context of problems with opioids. Interviews were audio-recorded, transcribed verbatim, and coded using Atlas.ti. RESULTS: Our analysis revealed seven areas of consideration for opioid agonist treatment decision-making: (1) awareness of treatment options; (2) expectations and goals for duration of treatment and abstinence; (3) prior experience with buprenorphine or methadone; (4) need for accountability and structured support; (5) preference to avoid methadone clinics or associated stigma; (6) fear of continued addiction and perceived difficulty of withdrawal; and (7) pain control. CONCLUSION: The availability of medication options increases the need for clear communication between clinicians and patients, for additional patient education about these medications, and for collaboration and patient influence over choices in treatment decision-making. Our results suggest that access to both methadone and buprenorphine will increase treatment options and patient choice and may enhance treatment adherence and outcomes.

Yeboah, J., Young, R., McClelland, R. L., Delaney, J. C., Polonsky, T. S., Dawood, F. Z., et al. (2016). Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. *Journal of the American College of Cardiology, 67*(2), 139-147.

BACKGROUND: The improvement in discrimination gained by adding nontraditional cardiovascular risk markers cited in the 2013 American College of Cardiology/American Heart Association cholesterol guidelines to the atherosclerotic cardiovascular disease (ASCVD) risk estimator (pooled cohort equation [PCE]) is untested. OBJECTIVES: This study assessed the predictive accuracy and improvement in reclassification gained by the addition of the coronary artery calcium (CAC) score, the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) levels, and family history (FH) of ASCVD to the PCE in participants of MESA (Multi-Ethnic Study of Atherosclerosis). METHODS: The PCE was calibrated (cPCE) and used for this analysis. The Cox proportional hazards survival model, Harrell's C statistics, and net reclassification improvement analyses were used. ASCVD was defined as myocardial infarction, coronary heart disease-related death, or fatal or nonfatal stroke. RESULTS: Of 6,814 MESA participants not prescribed statins at baseline, 5,185 had complete data and were included in this analysis. Their mean age was 61

years; 53.1% were women, 9.8% had diabetes, and 13.6% were current smokers. After 10 years of follow-up, 320 (6.2%) ASCVD events occurred. CAC score, ABI, and FH were independent predictors of ASCVD events in the multivariable Cox models. CAC score modestly improved the Harrell's C statistic (0.74 vs. 0.76; p = 0.04); ABI, hsCRP levels, and FH produced no improvement in Harrell's C statistic when added to the cPCE. CONCLUSIONS: CAC score, ABI, and FH were independent predictors of ASCVD events. CAC score modestly improved the discriminative ability of the cPCE compared with other nontraditional risk markers.

Young, K. H., Gough, M. J., & Crittenden, M. (2015). Tumor immune remodeling by TGFβ inhibition improves the efficacy of radiation therapy. *Oncoimmunology, 4*(3), 1-2.

The tumor immune environment has been linked to prognosis in patients with a range of malignancies. Recently, we demonstrated in pre-clinical models that modifying the tumor immune environment using a small-molecule inhibitor of TGFb significantly improved outcome to subsequent radiation therapy. These data suggest that this and other immunotherapies may be used to remodel the tumor before conventional cancer therapies to improve outcomes. © 2015 Taylor & Francis Group, LLC.

Yuen, K. C. J. (2014). Testosterone and cardiovascular disease: Controversy or wake-up call? *Cardiovascular Endocrinology, 3*(4), 117-122.

In men with hypogonadism due to diseases of the hypothalamus, pituitary, or testis, testosterone therapy is generally safe and has been shown to induce beneficial effects. Conversely, in men with age-related low testosterone levels, the significance of this change and the effects of testosterone therapy are debatable. Studies have linked low testosterone levels with increased cardiovascular morbidity and mortality, with testosterone therapy being reported to improve cardiovascular risk profiles. However, two recent retrospective studies have fueled the controversy on testosterone therapy by reporting increased cardiovascular events. Because placebo-controlled, randomized clinical trials on testosterone therapy in older men with age-related decline in testosterone levels are lacking, long-term cardiovascular health following testosterone therapy in this patient population remains unclear. Therefore, a careful approach should be adopted when considering therapy of hypogonadism and coexisting cardiovascular

disease in older men. Adequately powered, long-term prospective randomized trials on testosterone in older men are urgently needed. © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Yuen, K. C. J., Frystyk, J., Rhoads, S. A., & Bidlingmaier, M. (2016). Pegvisomant-primed glucagon stimulation test in assessing GH reserve and GH/IGF kinetics in adults suspected of GH deficiency. *Pituitary, 19*(1), 65-74.

Purpose: The accuracy of the glucagon stimulation test (GST) in diagnosing adult GH deficiency (GHD) has recently been questioned. Because pegvisomant (PegV) increases endogenous GH secretion, we hypothesized that priming PegV to the GST (PegV-GST) 72 h beforehand would improve the diagnostic accuracy of this test. This pilot study aimed to prospectively compare PegV-GST to two other diagnostic tests for adult GHD. Methods: Adults suspected of GHD underwent PegV-GST, GST and insulin tolerance test (ITT) in random order. Growth hormone levels (measured by a PegV insensitive assay) during PegV-GST, GST and ITT were compared, and acute effects of PegV on GH/IGF kinetics were assessed. Results: Ten subjects with hypothalamic-pituitary disease and 1–4 pituitary hormone deficiencies were studied. Basal and peak GH levels with the PegV-GST were comparable to those of the GST and ITT. The five subjects that failed the GST and ITT were the same subjects that failed the PegV-GST, using the peak GH cutpoint of <3 ng/mL for this test. After PegV priming, basal GH and GH binding protein (GHBP) increased (both $P < 0.01$) and total IGF-I and bioactive IGF decreased (both $P < 0.05$), whereas IGF-II and IGFBPs −1, −2 and −3 were unchanged compared to pre-PegV priming. Serum PegV levels correlated positively with basal GH, peak GH, IGFBP-1 and IGFBP-2 levels, and negatively with Δbioactive IGF and ΔGHBP (all $P < 0.05$). Conclusion: Single dose PegV administration in adults suspected of GHD increased basal GH and GHBP, with concomitant rapid fall in IGF-I levels and bioactive IGF. PegV priming did not appear to improve the diagnostic accuracy of the GST. Further studies involving larger subject numbers are needed to verify the clinical utility of PegV-GST in evaluating adult GHD. © 2015, Springer Science+Business Media New York.

Yun, H., Xie, F., Delzell, E., Levitan, E. B., Chen, L., Lewis, J. D., et al. (2016). Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in medicare. *Arthritis and Rheumatology, 68*(1), 56-66.

Objective The risks of hospitalized infection associated with biologic agents used to treat rheumatoid arthritis (RA) are unclear. The aim of this study was to determine whether the associated risk of hospitalized infections differed between specific biologic agents used to treat RA. Methods In a retrospective cohort study using Medicare data from 2006-2011 for all enrolled patients with RA, new episodes of treatment with etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept, rituximab, and tocilizumab were identified. Patients were required to have received another biologic agent previously and to have been continuously enrolled in Medicare medical and pharmacy plans during the baseline period and throughout followup. Followup started on the date of initiation of treatment with the new biologic agent (after previous treatment with a different biologic agent) and ended on the date of the earliest hospitalized infection, at 12 months, after an exposure gap of >30 days, or at the time of death or loss of Medicare coverage. Cox regression analysis was used to calculate the adjusted hazard ratio (HR) for hospitalized infection, adjusting for an infection risk score and other confounders. Results Of 31,801 new biologic treatment episodes in patients who had previously received another biologic agent, 12.0% were with etanercept, 15.2% with adalimumab, 5.9% with certolizumab, 4.4% with golimumab, 12.4% with infliximab, 28.9% with abatacept, 14.8% with rituximab, and 6.3% with tocilizumab. During followup, we identified 2,530 hospitalized infections; incidence rates ranged from 13.1 per 100 person-years (abatacept) to 18.7 per 100 person-years (rituximab). After adjustment, etanercept (HR 1.24, 95% confidence interval [95% CI] 1.07-1.45), infliximab (HR 1.39, 95% CI 1.21-1.60), and rituximab (HR 1.36, 95% CI 1.21-1.53) had significantly higher HRs for hospitalized infection compared with abatacept. Conclusion In RA patients with prior exposure to a biologic agent, exposure to etanercept, infliximab, or rituximab was associated with a greater 1-year risk of hospitalized infection compared with the risk associated with exposure to abatacept. © 2016, American College of Rheumatology.

Zhang, C., Bosch, M. A., Qiu, J., Ronnekleiv, O. K., & Kelly, M. J. (2015). 17beta-estradiol increases persistent na(+) current and excitability of AVPV/PeN Kiss1 neurons in female mice. *Molecular*

Endocrinology (Baltimore, Md.), 29(4), 518-527.

In vitro slice studies have revealed that there are significant differences in the spontaneous firing activity between anteroventral periventricular/periventricular preoptic nucleus (AVPV/PeN) and arcuate nucleus (ARC) kisspeptin (Kiss1) neurons in females. Although both populations express similar endogenous conductances, we have discovered that AVPV/PeN Kiss1 neurons express a subthreshold, persistent sodium current (INaP) that dramatically alters their firing activity. Based on whole-cell recording of Kiss1-Cre-green fluorescent protein (GFP) neurons, INaP was 4-fold greater in AVPV/PeN vs ARC Kiss1 neurons. An LH surge-producing dose of 17beta-estradiol (E2) that increased Kiss1 mRNA expression in the AVPV/PeN, also augmented INaP in AVPV/PeN neurons by 2-fold. Because the activation threshold for INaP was close to the resting membrane potential (RMP) of AVPV/PeN Kiss1 neurons (-54 mV), it rendered them much more excitable and spontaneously active vs ARC Kiss1 neurons (RMP = -66 mV). Single-cell RT-PCR revealed that AVPV/PeN Kiss1 neurons expressed the requisite sodium channel alpha-subunit transcripts, NaV1.1, NaV1.2, and NaV1.6 and beta subunits, beta2 and beta4. Importantly, NaV1.1alpha and -beta2 transcripts in AVPV/PeN, but not ARC, were up-regulated 2- to 3-fold by a surge-producing dose of E2, similar to the transient calcium current channel subunit Cav3.1. The transient calcium current collaborates with INaP to generate burst firing, and selective blockade of INaP by riluzole significantly attenuated rebound burst firing and spontaneous activity. Therefore, INaP appears to play a prominent role in AVPV/PeN Kiss1 neurons to generate spontaneous, repetitive burst firing, which is required for the high-frequency-stimulated release of kisspeptin for exciting GnRH neurons and potentially generating the GnRH surge.

Zhang, C., Meermeier, N. P., Terker, A. S., Blankenstein, K. I., Singer, J. D., Hadchouel, J., et al. (2016). Degradation by cullin 3 and effect on WNK kinases suggest a role of KLHL2 in the pathogenesis of familial hyperkalemic hypertension. *Biochemical and Biophysical Research Communications, 469*(1), 44-48.

Mutations in WNK1 and WNK4, and in components of the Cullin-Ring Ligase system, kelch-like 3 (KLHL3) and Cullin 3 (CUL3), can cause the rare hereditary disease, Familial Hyperkalemic Hypertension (FHHt). The disease is characterized by overactivity of the renal sodium chloride cotransporter (NCC), which is phosphorylated and activated by the WNK-stimulated Ste20-type

kinases, SPAK and OSR1. WNK kinases themselves can be targeted for ubiquitination and degradataion by the CUL3-KLHL3 E3 ubiquitin ligase complex. It is unclear, however, why there are significant differences in phenotypic severity among FHHt patients with mutations in different genes. It was reported that kelch-like 2 (KLHL2), a homolog of KLHL3, can also target WNK kinases for ubiquitation and degradation, and may play a special role in the systemic vasculature. Our recent study revealed the disease mutant CUL3 exhibits enhanced degradation of its adaptor protein KLHL3, potentially resulting in accumulation of WNK kinases secondarily. To investigate if KLHL2 plays a role in FHHt, we studied the effect of wild type and FHHt mutant CUL3 on degradation of KLHL2 and WNK kinase proteins in HEK293 cells. Although CUL3 facilitates KLHL2 degradation, the disease mutant CUL3 is more active in this regard. KLHL2 facilitated the degradation of wild type but not disease mutant WNK4 protein. These results suggest that KLHL2 likely plays a role in the pathogenesis of FHHt, and aggravates the phenotype caused by mutations in CUL3 and WNK4.

Zhen, J., Antonio, T., Jacob, J. C., Grandy, D. K., Reith, M. E. A., Dutta, A. K., et al. (2015). Efficacy of hybrid tetrahydrobenzo[d]thiazole based aryl piperazines D-264 and D-301 at D2 and D3 receptors. *Neurochemical Research,* , 1-12.

In elucidating the role of pharmacodynamic efficacy at D3 receptors in therapeutic effectiveness of dopamine receptor agonists, the influence of study system must be understood. Here two compounds with D3 over D2 selectivity developed in our earlier work, D-264 and D-301, are compared in dopamine receptor-mediated G-protein activation in striatal regions of wild-type and D2 receptor knockout mice and in CHO cells expressing D2 or D3 receptors. In caudate-putamen of D2 knockout mice, D-301 was ~3-fold more efficacious than D-264 in activating G-proteins as assessed by [35S]GTPγS binding; in nucleus accumbens, D-301 stimulated G-protein activation whereas D-264 did not. In contrast, the two ligands exerted similar efficacy in both regions of wild-type mice, suggesting both ligands activate D2 receptors with similar efficacy. In D2 and D3 receptor-expressing CHO cells, D-264 and D-301 appeared to act in the [35S]GTPγS assay as full agonists because they produced maximal stimulation equal to dopamine. Competition for [3H]spiperone binding was then performed to determine Ki/EC50 ratios as an index of receptor reserve for each ligand. Action of D-301, but not D-264, showed receptor reserve in D3 but not in

D2 receptor-expressing cells, whereas dopamine showed receptor reserve in both cell lines. Gαo1 is highly expressed in brain and is important in D2-like receptor-G protein coupling. Transfection of Gαo1 in D3- but not D2-expressing CHO cells led to receptor reserve for D-264 without altering receptor expression levels. D-301 and dopamine exhibited receptor reserve in D3-expressing cells both with and without transfection of Gαo1. Altogether, these results indicate that D-301 has greater intrinsic efficacy to activate D3 receptors than D-264, whereas the two compounds act on D2 receptors with similar intrinsic efficacy. These findings also suggest caution in interpreting Emax values from functional assays in receptor-transfected cell models without accounting for receptor reserve. © 2015 Springer Science+Business Media New York

Zilberman-Rudenko, J., Itakura, A., Wiesenekker, C. P., Vetter, R., Maas, C., Gailani, D., et al. (2016). Coagulation factor XI promotes distal platelet activation and single platelet consumption in the bloodstream under shear flow. *Arteriosclerosis, Thrombosis, and Vascular Biology,* OBJECTIVE—: Coagulation factor XI (FXI) has been shown to contribute to thrombus formation on collagen or tissue factor–coated surfaces in vitro and in vivo by enhancing thrombin generation. Whether the role of the intrinsic pathway of coagulation is restricted to the local site of thrombus formation is unknown. This study was aimed to determine whether FXI could promote both proximal and distal platelet activation and aggregate formation in the bloodstream. APPROACH AND RESULTS—: Pharmacological blockade of FXI activation or thrombin activity in blood did not affect local platelet adhesion, yet reduced local platelet aggregation, thrombin localization, and fibrin formation on immobilized collagen and tissue factor under shear flow, ex vivo. Downstream of the thrombus formed on immobilized collagen or collagen and 10 pmol/L tissue factor, platelet CD62P expression, microaggregate formation, and progressive platelet consumption were significantly reduced in the presence of FXI function-blocking antibodies or a thrombin inhibitor in a shear rate– and time-dependent manner. In a non-human primate model of thrombus formation, we found that inhibition of FXI reduced single platelet consumption in the bloodstream distal to a site of thrombus formation. CONCLUSIONS—: This study demonstrates that the FXI–thrombin axis contributes to distal platelet activation and procoagulant microaggregate formation in the blood flow downstream of the site of thrombus formation. Our

data highlight FXI as a novel therapeutic target for inhibiting distal thrombus formation without affecting proximal platelet adhesion. © 2016 American Heart Association, Inc.

Zuloaga, D. G., Johnson, L. A., Weber, S., & Raber, J. (2016). Immediate and lasting effects of chronic daily methamphetamine exposure on activation of cells in hypothalamic-pituitary-adrenal axis-associated brain regions. *Psychopharmacology, 233*(3), 381-392.

Rationale: Chronic methamphetamine (MA) abuse leads to dependence and symptoms of withdrawal after use has ceased. Negative mood states associated with withdrawal, as well as drug reinstatement, have been linked to drug-induced disruption of the hypothalamic-pituitary-adrenal (HPA) axis. However, effects of chronic MA exposure or acute MA exposure following withdrawal on neural activation patterns within brain regions that regulate the HPA axis are unknown. Objectives: In this study, neural activation patterns were assessed by quantification of c-Fos protein in mice exposed to different regimens of MA administration. Methods: (Experiment 1) Adult male mice were treated with MA (5 mg/kg) or saline once or once daily for 10 days. (Experiment 2) Mice were treated with MA or saline once daily for 10 days and following a 10-day withdrawal period were re-administered a final dose of MA or saline. c-Fos was quantified in brains after the final injection. Results: (Experiment 1) Compared to exposure to a single dose of MA (5 mg/kg), chronic MA exposure decreased the number of c-Fos expressing cells in the paraventricular hypothalamus, dorsomedial hypothalamus, central amygdala, basolateral amygdala, bed nucleus of the stria terminalis (BNST), and CA3 hippocampal region. (Experiment 2) Compared to mice receiving their first dose of MA, mice chronically treated with MA, withdrawn, and re-administered MA, showed decreased c-Fos expressing cells within the central and basolateral amygdala, BNST, and CA3. Conclusions: HPA axis-associated amygdala, extended amygdala, and hippocampal regions endure lasting effects following chronic MA exposure and therefore may be linked to stress-related withdrawal symptoms. © 2015 Springer-Verlag Berlin Heidelberg.

Zuloaga, D. G., Lahvis, G. P., Mills, B., Pearce, H. L., Turner, J., & Raber, J. (2016). Fetal domoic acid exposure affects lateral amygdala neurons, diminishes social investigation and alters sensory-motor gating. *Neurotoxicology, 53*, 132-140.

Domoic acid (DA) is an algal neurotoxin that accumulates in marine fish and shellfish. DA can move across the placenta and concentrate in amniotic fluid, which can be swallowed during late gestation. DA also transfers to infants via milk. Preclinical studies to determine effects of developmental DA expose have primarily involved DA exposure during the postnatal period and little is known about late CNS effects following prenatal DA. In the present study, we tested the hypothesis that prenatal exposure of FVB mice to low levels of DA would result in diminished social interaction and sensory motor gating associated with alterations in parvalbumin immunoreactivity in relevant brain regions undergoing development during and following DA exposure. In addition to parvalbumin, we stained with NeuN for a neuronal specific nuclear protein to determine if neuronal loss followed prenatal DA exposure. A single moderate dose of DA administered during gestation produces diminishes social investigation and alters sensorimotor gating, behavioral effects more pronounced in males than females. These behavioral changes were associated with discrete alterations in the parvalbumin-positive subtype of GABAergic neurons in the dentate gyrus and lateral amygdala.

Zwald, F., Leitenberger, J., Zeitouni, N., Soon, S., Brewer, J., Arron, S., et al. (2016). Recommendations for solid organ transplantation for transplant candidates with a pretransplant diagnosis of cutaneous squamous cell carcinoma, merkel cell carcinoma and melanoma: A consensus opinion from the international transplant skin cancer collaborative (ITSCC). *American Journal of Transplantation : Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 16*(2), 407-413.

Advancements in solid organ transplantation successfully extend the lives of thousands of patients annually. The tenet of organ stewardship aims to prevent the futile expenditure of scarce donor organs in patient populations with high mortality risk, to the detriment of potential recipients with greater predicted life expectancy. The development of skin cancer posttransplantation portends tremendous morbidity, adversely affecting quality of life for many transplant recipients. This special article, provided by of members of the International Transplant Skin Cancer Collaborative (ITSCC), will provide the transplant professional with a consensus opinion and recommendations as to an appropriate wait period pretransplantation for transplant

candidates with a history of either cutaneous squamous cell carcinoma, malignant melanoma, or Merkel cell carcinoma.