References

Ahmann, A., Rodbard, H. W., Rosenstock, J., Lahtela, J. T., de Loredo, L., Tornoe, K., et al. (2015). Efficacy and safety of liraglutide vs. placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: A randomized, placebo-controlled trial. *Diabetes, Obesity & Metabolism,*

OBJECTIVE: Confirm superiority of adding liraglutide vs. placebo to pre-existing basal insulin analogue +/- metformin in adults with inadequately controlled type 2 diabetes (HbA1c 7.0-10.0% [53-86 mmol/mol]). MATERIALS AND METHODS: In this 26-week, double-blind, parallel-group trial conducted in clinics or hospitals, 451 subjects were randomized 1:1 to once-daily liraglutide 1.8 mg (dose escalated from 0.6 and 1.2 mg/day, respectively, for 1 week each) (n=226) or placebo (n=225) added to their pre-existing basal insulin analogue (>/=20 U/day) +/- metformin (>/=1500 mg/day). Following randomization, insulin adjustments above the pre-trial dose were not allowed. Primary endpoint was HbA1c change. RESULTS: After 26 weeks, HbA1c decreased more with liraglutide (-1.3% [-14.2 mmol/mol]) than placebo (-0.1% [-1.2 mmol/mol]); p<0.0001. More subjects on liraglutide reached HbA1c targets: <7.0% (59 vs. 14%; p<0.0001) and </=6.5% (43 vs. 4%; p<0.0001) using slightly less insulin (35.8 vs. 40.1 IU). Greater decreases from baseline (estimated treatment differences vs. placebo; p<0.0001) occurred in fasting plasma glucose (-1.3 mmol/l), 7-point glucose profiles (-1.6 mmol/l), body weight (-3.1 kg) and systolic blood pressure (SBP) (-5.0 mmHg). Transient gastrointestinal adverse events (nausea: 22.2 vs. 3.1%) and minor hypoglycaemia (18.2 vs. 12.4%) were more frequent with liraglutide than placebo, and pulse increased (4.5 beats/min) compared with placebo. No severe hypoglycaemia or pancreatitis occurred. CONCLUSIONS: Adding liraglutide to a basal insulin analogue +/- metformin significantly improved glycaemic control, body weight and SBP vs. placebo. Typical gastrointestinal symptoms and minor hypoglycaemia were more frequent with liraglutide.

Aicher, S. A., Hermes, S. M., & Hegarty, D. M. (2013). Corneal afferents differentially target thalamic- and parabrachial-projecting neurons in spinal trigeminal nucleus caudalis. *Neuroscience, 232*, 182-193.

Dorsal horn neurons send ascending projections to both thalamic nuclei and parabrachial nuclei;

these pathways are thought to be critical pathways for central processing of nociceptive information. Afferents from the corneal surface of the eye mediate nociception from this tissue which is susceptible to clinically important pain syndromes. This study examined corneal afferents to the trigeminal dorsal horn and compared inputs to thalamic- and parabrachial-projecting neurons. We used anterograde tracing with cholera toxin B subunit to identify corneal afferent projections to trigeminal dorsal horn, and the retrograde tracer FluoroGold to identify projection neurons. Studies were conducted in adult male Sprague-Dawley rats. Our analysis was conducted at two distinct levels of the trigeminal nucleus caudalis (Vc) which receive corneal afferent projections. We found that corneal afferents project more densely to the rostral pole of Vc than the caudal pole. We also quantified the number of thalamic- and parabrachial-projecting neurons in the regions of Vc that receive corneal afferents. Corneal afferent inputs to both groups of projection neurons were also more abundant in the rostral pole of Vc. Finally, by comparing the frequency of corneal afferent appositions to thalamic- versus parabrachial-projecting neurons, we found that corneal afferents preferentially target parabrachial-projecting neurons in trigeminal dorsal horn. These results suggest that nociceptive pain from the cornea may be primarily mediated by a non-thalamic ascending pathway.

Alonso, E., Aramendi, E., González-Otero, D., Ayala, U., Daya, M., & Russell, J. K. (2014). Empirical mode decomposition for chest compression and ventilation detection in cardiac arrest. *41st Computing in Cardiology Conference, CinC 2014, , 41.* (January) pp. 17-20.
The thoracic impedance (TI) signal, which reflects fluctuations due to CCs and ventilations, has been suggested as a surrogate to compute CC-rate and ventilation-rate during cardiopulmonary resuscitation. This study developed a method based on empirical mode decomposition (EMD) to compute CC-rate and ventilation-rate using exclusively the TI. Twenty out-of-hospital cardiac arrest episodes containing the TI, compression depth (gold standard for CC-rate), and capnography (gold standard for ventilation-rate) signals were used. The EMD decomposed the TI signal into intrinsic mode functions (IMFs). IMFs were combined based on their median instantaneous frequency to reconstruct separately the CC-signal and the ventilation-signal. Independent CC and ventilation detectors were used based on fixed thresholds for durations and dynamic thresholds for the amplitudes of the fluctuations. Sensitivity and positive predictive

value (PPV) for each detector were 99.35%/98.75% and 93.21%/82.40%. CC-rate and ventilation-rate were computed based on instants of CCs and ventilations respectively. When comparing detected rates with rates obtained from the gold standards, the mean (SD) errors were 0.57(0.55) min-1 and 1.10 (1.19) min -1 for CC-rate and ventilation-rate respectively. We concluded that CC-rate and ventilation-rate can be accurately estimated applying EMD to the TI.

Amaral, A. F., Coton, S., Kato, B., Tan, W. C., Studnicka, M., Janson, C., et al. (2015). Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *The European Respiratory Journal,*
In small studies and cases series, a history of tuberculosis has been associated with both airflow obstruction, which is characteristic of chronic obstructive pulmonary disease, and restrictive patterns on spirometry. The objective of the present study was to assess the association between a history of tuberculosis and airflow obstruction and spirometric abnormalities in adults.The study was performed in adults, aged 40 years and above, who took part in the multicentre, cross-sectional, general population-based Burden of Obstructive Lung Disease study, and had provided acceptable post-bronchodilator spirometry measurements and information on a history of tuberculosis. The associations between a history of tuberculosis and airflow obstruction and spirometric restriction were assessed within each participating centre, and estimates combined using meta-analysis. These estimates were stratified by high- and low/middle-income countries, according to gross national income.A self-reported history of tuberculosis was associated with airflow obstruction (adjusted odds ratio 2.51, 95% CI 1.83-3.42) and spirometric restriction (adjusted odds ratio 2.13, 95% CI 1.42-3.19).A history of tuberculosis was associated with both airflow obstruction and spirometric restriction, and should be considered as a potentially important cause of obstructive disease and low lung function, particularly where tuberculosis is common.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). Rifm fragrance ingredient safety assessment, (2E,6Z)-nona-2,6-dien-1-ol, CAS registry number 28069-72-9. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). Rifm fragrance ingredient safety assessment, (Z)-2-penten-1-ol, CAS registry number 1576-95-0. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, isophytol, CAS registry number 505-32-8. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, benzyl acetate, CAS registry number 140-11-4. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Baptista, A. M. (2015). The power of estuarine collaboratories. *2015 IEEE Underwater Technology, UT 2015,*
Developing science-based strategies to best balance estuarine use and resilience is critical to a sustainable earth, but is also challenging. To meet the challenge, we created for the Columbia River estuary, in the United States, a distinctive scientific infrastructure that we term 'collaboratory.' We define collaboratory as a networked integration of sensors, platforms, models, data, analyses, and collaboration & social processes, designed to enable diverse communities of practice to interact without geographic, disciplinary or institutional barriers, towards scientific understanding, prediction, operation and sustainability of estuaries and coastal margins. This paper introduces our collaboratory, synthesizes lessons learned, and introduces a vision for possible replication to a global network of estuaries. © 2015 IEEE.

Barton, C. A., Johnson, N. B., Case, J., Warden, B., Hughes, D., Zimmerman, J., et al. (2015). Risk of thromboembolic events after protocolized warfarin reversal with 3-factor prothrombin complex concentrate and factor VIIa. *The American Journal of Emergency Medicine,*
Bleeding events and life-threatening hemorrhage are the most feared complications of warfarin

therapy. Prompt anticoagulant reversal aimed at replacement of vitamin K-dependent clotting factors is essential to promote hemostasis. A retrospective cohort study of warfarin-treated patients experiencing a life-threatening hemorrhage treated with an institution-specific warfarin reversal protocol (postimplementation group) and those who received the prior standard of care (preimplementation group) was performed. The reversal protocol included vitamin K, 3-factor prothrombin complex concentrate, and recombinant factor VIIa. Demographic and clinical information, anticoagulant reversal information, and all adverse events attributed to warfarin reversal were recorded. A total of 227 patients were included in final analysis, 109 in the preimplementation group and 118 in the postimplementation group. Baseline patient characteristics were similar in both groups, with the exception of higher average Sequential Organ Failure Assessment scores in the postimplementation group (P = .0005). The most common indication for anticoagulation reversal was intraparenchymal hemorrhage. Prereversal international normalized ratios (INRs) were similar in both groups. Attainment of INR normalization to less than 1.4 was higher, and rebound INR was lower in the postimplementation group (P < .0001; P = .0013). Thromboembolic complications were significantly higher in the postimplementation group (P = .003). Elevated baseline Sequential Organ Failure Assessment score and mechanical valve as an indication for anticoagulation were independently associated with thrombotic complications (P = .005). A warfarin reversal protocol consisting of 3-factor prothrombin complex concentrate, recombinant factor VIIa, and vitamin K more consistently normalized INR values to less than 1.4 as compared to the prior standard of care in a diverse patient population. This success came at the cost of a 2-fold increase in risk of thromboembolic complications.

Baugh, C. W., Liang, L. J., Probst, M. A., & Sun, B. C. (2015). National cost savings from observation unit management of syncope. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine,*

OBJECTIVES: Syncope is a frequent emergency department (ED) presenting complaint and results in a disproportionate rate of hospitalization with variable management strategies. The objective was to estimate the annual national cost savings, reduction in inpatient hospitalizations, and reduction in hospital bed hours from implementation of protocolized care in an observation

unit. METHODS: We created a Monte Carlo simulation by building a model that reflects current clinical practice in the United States and uses inputs gathered from the most recent available peer-reviewed literature and national survey data. ED visit volume was adjusted to reflect observation unit availability and the portion of observation visits requiring subsequent inpatient care. A recent multicenter randomized controlled study informed the cost savings and length of stay reduction per observation unit visit model inputs. The study population included patients aged 50 years and older with syncope deemed at intermediate risk for serious 30-day cardiovascular outcomes. RESULTS: The mean (+/-SD) annual cost savings was estimated to be $108 million (+/-$89 million) from avoiding 235,000 (+/-13,900) inpatient admissions, resulting in 4,297,000 (+/-1,242,000) fewer hospital bed hours. CONCLUSIONS: The potential national cost savings for managing selected patients with syncope in a dedicated observation unit is substantial. Syncope is one of many conditions suitable for care in an observation unit as an alternative to an inpatient setting. As pressure to decrease hospital length of stay and bill short-stay hospitalizations as observation increases, syncope illustrates the value of observation unit care.

Bayer, L. L., Edelman, A. B., Fu, R., Lambert, W. E., Nichols, M. D., Bednarek, P. H., et al. (2015). An evaluation of oral midazolam for anxiety and pain in first-trimester surgical abortion. *Obstetrics and Gynecology, 126*(1), 37-46.

Objective: To estimate the effect of oral midazolam on patient pain and anxiety perception during first-trimester surgical abortion. Methods: Between May and December 2013, we conducted a randomized, double-blind, placebo-controlled trial. Patients between 6 0/7 and 10 6/7 weeks of gestation received 10 mg oral midazolam or placebo 30-60 minutes before surgical abortion. All patients received ibuprofen and a paracervical block. We powered the study (power80%; significance level.025) to detect a 15-mm difference in our two a priori primary outcomes of pain and anxiety with uterine aspiration on a 100-mm visual analog scale. Secondary outcomes were pain and anxiety at additional time points, memory, satisfaction, side effects, and adverse events. Results: Demographics were similar between groups (placebo62, midazolam62). Compared with those randomized to placebo, patients who received midazolam had significantly less anxiety preoperatively (room entry: 51.4 mm compared with 34.5 mm, P<.001; positioning:

56.6 mm compared with 45.4 mm, P.02). There was no difference in pain (P.28) or anxiety

(P.14) during uterine aspiration or at other procedural time points. A significantly greater number

of patients in the midazolam group reported partial amnesia (31/61 compared with 16/61, P.005)

and dizziness (30/61 compared with 18/61, P.03). Controlling for baseline differences, patients

who received midazolam reported more postoperative sleepiness (P<.001) and less postoperative

nausea (P.004). There was no difference in overall satisfaction (P.88). Conclusion: Although oral

midazolam reduces preprocedural anxiety, it does not reduce pain or anxiety with uterine

aspiration during first-trimester surgical abortions. © 2015 by The American College of

Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.

Bazemore, A. W., Cottrell, E. K., Gold, R., Hughes, L. S., Phillips, R. L., Angier, H., et al. (2015).

"Community vital signs": Incorporating geocoded social determinants into electronic records to

promote patient and population health. *Journal of the American Medical Informatics Association :*

JAMIA,

Social determinants of health significantly impact morbidity and mortality; however, physicians

lack ready access to this information in patient care and population management. Just as

traditional vital signs give providers a biometric assessment of any patient, "community vital

signs" (Community VS) can provide an aggregated overview of the social and environmental

factors impacting patient health. Knowing Community VS could inform clinical recommendations

for individual patients, facilitate referrals to community services, and expand understanding of

factors impacting treatment adherence and health outcomes. This information could also help

care teams target disease prevention initiatives and other health improvement efforts for clinic

panels and populations. Given the proliferation of big data, geospatial technologies, and

democratization of data, the time has come to integrate Community VS into the electronic health

record (EHR). Here, the authors describe (i) historical precedent for this concept, (ii)

opportunities to expand upon these historical foundations, and (iii) a novel approach to EHR

integration.

Beauchamp, G. A. (2015). The toxicologist as educator: Addressing pain management in the midst of an opioid epidemic. *Journal of Medical Toxicology : Official Journal of the American College of Medical Toxicology,*

Bennett, R. M. (2014). Guidelines for the successful management of fibromyalgia patients. *Indian Journal of Rheumatology, 9*(S2), S13-S21.

The successful management of fibromyalgia starts with establishing a firm diagnosis, followed by an evaluation of all other comorbid pain conditions (e.g. osteoarthritis, temporomandibular pain disorder, migraine headaches, myofascial trigger points) and fibromyalgia associated comorbidities (e.g. restless leg syndrome, irritable bowel syndrome). Then, it is necessary to systematically go through a list of problems that need to be addressed: pain, sleep, fatigue, mood disorders, cognitive dysfunction, functional limitations, social functioning, prior therapies and expectations. The most fundamental issue in successful management is initiating patient directed therapies. This involves education regarding the nature of fibromyalgia, the various tools for treating different aspects of the disorder and the development of a constructive and flexible treatment program that will be modified according to the results. All fibromyalgia patients should be given a trial of medications that have been shown to help pain. Non-restorative sleep diminishes the effectiveness of the descending inhibitory pain pathway, thus effective treatment is an essential component of pain management, as well as helping fatigue and cognition. It is important to rule out treatable associated sleep disruptors such as restless legs syndrome and sleep apnea. The basis of attaining effective sleep is the patient's adherence to basic sleep hygiene measures. Cognitive behavioral therapy where feasible, should be pursued. Ideally, hypnotics should be used as a short-term bridge while the patient is establishing behavioral modifications. Regular gentle exercise has repeatedly been shown to benefit fibromyalgia patients and needs to be incorporated in every patient's management strategy. Practicing mindfulness is a useful strategy for minimizing stress and can be incorporated into gentle exercise in the form of yoga and Tai chi. Having fibromyalgia creates an existential crisis for most patients, the management of these clients can be a rewarding experience for the well-informed and empathetic physician. Copyright © 2014, Indian Rheumatology Association. All rights reserved.

Bennett, T. A., Szatmari, P., Georgiades, K., Hanna, S., Janus, M., Georgiades, S., et al. (2015). Do

reciprocal associations exist between social and language pathways in preschoolers with autism

spectrum disorders? *Journal of Child Psychology and Psychiatry and Allied Disciplines, 56*(8),

874-883.

Background Differences in how developmental pathways interact dynamically in children with

autism spectrum disorder (ASD) likely contribute in important ways to phenotypic heterogeneity.

This study aimed to model longitudinal reciprocal associations between social competence (SOC)

and language (LANG) pathways in young children with ASD. Methods Data were obtained from

365 participants aged 2-4 years who had recently been diagnosed with an ASD and who were

followed over three time points: baseline (time of diagnosis), 6- and 12 months later. Using

structural equation modeling, a cross-lagged reciprocal effects model was developed that

incorporated auto-regressive (stability) paths for SOC (using the Socialization subscale of the

Vineland Adaptive Behavior Scales-2) and LANG (using the Preschool Language Scale-4 Auditory

Comprehension subscale). Cross-domain associations included within-time correlations and

lagged associations. Results SOC and LANG were highly stable over 12 months. Small reciprocal

cross-lagged associations were found across most time points and within-time correlations

decreased over time. There were no differences in strength of cross-lagged associations between

SOC-LANG and LANG-SOC across time points. Few differences were found between subgroups of

children with ASD with and without cognitive impairment. Conclusions Longitudinal reciprocal

cross-domain associations between social competence and language were small in this sample of

young children with ASD. Instead, a pattern emerged to suggest that the two domains were

strongly associated around time of diagnosis in preschoolers with ASD, and then appeared to

become more independent over the ensuing 12 months. © 2014 Association for Child and

Adolescent Mental Health.

Bhattacharya, S., Wheeler, H., Leid, M., Ganguli-Indra, G., & Indra, A. K. (2015). Transcription factor

CTIP2 maintains hair follicle stem cell pool and contributes to altered expression of LHX2 and

NFATC1. *The Journal of Investigative Dermatology,*

Transcription factor CTIP2 (COUP-TF-interacting protein 2), also known as BCL11B, is expressed

in hair follicles of embryonic and adult skin. Ctip2-null mice exhibit reduced hair follicle density

during embryonic development. In contrast, conditional inactivation of Ctip2 in epidermis (Ctip2ep-/- mice) leads to a shorter telogen and premature entry into anagen during the second phase of hair cycling without a detectable change in the number of hair follicles. Keratinocytes of the bulge stem cells niche of Ctip2ep-/- mice proliferate more and undergo reduced apoptosis than the corresponding cells of wild-type mice. However, premature activation of follicular stem cells in mice lacking CTIP2 leads to the exhaustion of this stem cell compartment in comparison to Ctip2L2/L2mice, which retained quiescent follicle stem cells. CTIP2 modulates expression of genes encoding EGFR and NOTCH1 during formation of hair follicles, and those encoding NFATC1 and LHX2 during normal hair cycling in adult skin. The expression of most of these genes is disrupted in mice lacking CTIP2 and these alterations may underlie the phenotype of Ctip2-null and Ctip2ep-/- mice. CTIP2 appears to serve as a transcriptional organizer that integrates input from multiple signaling cues during hair follicle morphogenesis and hair cycling.Journal of Investigative Dermatology accepted article preview online, 15 July 2015. doi:10.1038/jid.2015.281.

Blackburn, N. J., Yan, N., & Lutsenko, S. (2014). In Maret W., &Wedd A.(Eds.), *Copper in eukaryotes* Royal Society of Chemistry.

Blanke, C. D., & Fromme, E. K. (2015). Chemotherapy near the end of life: First-and third and fourth (line)-do no harm. *JAMA Oncology,*

Bleyer, A. (2015). The death burden and end-of-life care intensity among adolescent and young adult patients with cancer. *JAMA Oncology,*

Bolon-Canedo, V., Ataer-Cansizoglu, E., Erdogmus, D., Kalpathy-Cramer, J., Fontenla-Romero, O., Alonso-Betanzos, A., et al. (2015). Dealing with inter-expert variability in retinopathy of prematurity: A machine learning approach. *Computer Methods and Programs in Biomedicine,* BACKGROUND AND OBJECTIVE: Understanding the causes of disagreement among experts in clinical decision making has been a challenge for decades. In particular, a high amount of variability exists in diagnosis of retinopathy of prematurity (ROP), which is a disease affecting low birth weight infants and a major cause of childhood blindness. A possible cause of variability, that

has been mostly neglected in the literature, is related to discrepancies in the sets of important features considered by different experts. In this paper we propose a methodology which makes use of machine learning techniques to understand the underlying causes of inter-expert variability. METHODS: The experiments are carried out on a dataset consisting of 34 retinal images, each with diagnoses provided by 22 independent experts. Feature selection techniques are applied to discover the most important features considered by a given expert. Those features selected by each expert are then compared to the features selected by other experts by applying similarity measures. Finally, an automated diagnosis system is built in order to check if this approach can be helpful in solving the problem of understanding high inter-rater variability. RESULTS: The experimental results reveal that some features are mostly selected by the feature selection methods regardless the considered expert. Moreover, for pairs of experts with high percentage agreement among them, the feature selection algorithms also select similar features. By using the relevant selected features, the classification performance of the automatic system was improved or maintained. CONCLUSIONS: The proposed methodology provides a handy framework to identify important features for experts and check whether the selected features reflect the pairwise agreements/disagreements. These findings may lead to improved diagnostic accuracy and standardization among clinicians, and pave the way for the application of this methodology to other problems which present inter-expert variability.

Bonnemaison, M. L., Back, N., Duffy, M. E., Ralle, M., Mains, R. E., & Eipper, B. A. (2015). Adaptor protein-1 complex affects the endocytic trafficking and function of peptidylglycine alpha-amidating monooxygenase, a luminal cuproenzyme. *The Journal of Biological Chemistry,*
The adaptor protein-1 complex (AP-1), which transports cargo between the trans-Golgi network and endosomes, plays a role in the trafficking of Atp7a, a copper-transporting P-type ATPase, and peptidylglycine alpha-amidating monooxygenase (PAM), a copper-dependent membrane enzyme. Lack of any of the four AP-1 subunits impairs function and patients with MEDNIK syndrome, a rare genetic disorder caused by lack of expression of the sigma1A subunit, exhibit clinical and biochemical signs of impaired copper homeostasis. To explore the role of AP-1 in copper homeostasis in neuroendocrine cells, we used corticotrope tumor cells in which AP-1 function was diminished by reducing expression of its mu1A subunit. Copper levels were unchanged when AP-1

function was impaired, but cellular levels of Atp7a declined slightly. The ability of PAM to function was assessed by monitoring 18K Fragment-NH2 production from proopiomelanocortin. Reduced AP-1 function made 18K Fragment amidation more sensitive to inhibition by bathocuproine disulfonate, a cell-impermeant Cu(I) chelator. The endocytic trafficking of PAM was altered and PAM-1 accumulated on the cell surface when AP-1 levels were reduced. Reduced AP-1 function increased Atp7a presence in early/recycling endosomes but did not alter the ability of copper to stimulate its appearance on the plasma membrane. Co-immunoprecipitation of a small fraction of PAM and Atp7a supports the suggestion that copper can be transferred directly from Atp7a to PAM, a process which can occur only when both proteins are present in the same subcellular compartment. Altered luminal cuproenzyme function may contribute to deficits observed when AP-1 function is compromised.

Bowen, J. L., Hirsh, D., Aagaard, E., Kaminetzky, C. P., Smith, M., Hardman, J., et al. (2015). Advancing educational continuity in primary care residencies: An opportunity for patient-centered medical homes. *Academic Medicine : Journal of the Association of American Medical Colleges, 90*(5), 587-593.

Continuity of care is a core value of patients and primary care physicians, yet in graduate medical education (GME), creating effective clinical teaching environments that emphasize continuity poses challenges. In this Perspective, the authors review three dimensions of continuity for patient care-informational, longitudinal, and interpersonal-and propose analogous dimensions describing continuity for learning that address both residents learning from patient care and supervisors and interprofessional team members supporting residents' competency development. The authors review primary care GME reform efforts through the lens of continuity, including the growing body of evidence that highlights the importance of longitudinal continuity between learners and supervisors for making competency judgments. The authors consider the challenges that primary care residency programs face in the wake of practice transformation to patient-centered medical home models and make recommendations to maximize the opportunity that these practice models provide. First, educators, researchers, and policy makers must be more precise with terms describing various dimensions of continuity. Second, research should prioritize developing assessments that enable the study of the impact of interpersonal continuity on clinical

outcomes for patients and learning outcomes for residents. Third, residency programs should establish program structures that provide informational and longitudinal continuity to enable the development of interpersonal continuity for care and learning. Fourth, these educational models and continuity assessments should extend to the level of the interprofessional team. Fifth, policy leaders should develop a meaningful recognition process that rewards academic practices for training the primary care workforce.

Britton, J., & Bloom, J. D. (2015). Oregon's gun relief program for adjudicated mentally ill persons: The psychiatric security review board. *Behavioral Sciences and the Law, 33*(2-3), 323-333. This article describes the State of Oregon's implementation of two programs designed to comply with federal gun laws regarding reporting individuals who have received mental health adjudications in criminal and civil courts. One mandate requires that states submit names of adjudicated individuals to the National Instant Criminal Background Check System (NICS) while the second requires that the state establish a qualifying gun restoration program for those disqualified from gun ownership. In 2009, Oregon's Legislature developed an administrative approach to gun restoration and assigned the responsibility for conducting these hearing to the Oregon Psychiatric Security Review Board (PSRB). The PSRB is a state administrative board that has existed since 1977 and has been primarily focused on the supervision and treatment of adult and juvenile insanity acquittees. The gun restoration program began in 2010, but to date has only received three completed petitions requesting restoration of firearm rights. The article concludes with a discussion that surmises why very few of the Oregonians who are listed in NICS have submitted petitions for relief. © 2015 John Wiley & Sons, Ltd.

Broberg, C. S. (2014). Cardiac magnetic imaging of the patient with an atrial switch palliation for transposition of the great arteries. *Progress in Pediatric Cardiology, 38*(1-2), 49-55. Patients with transposition of the great arteries treated with either a Mustard or Senning atrial switch palliation are often referred for assessment with cardiovascular magnetic resonance (CMR). Frequent indications for scanning include quantifying systemic right ventricular function, assessing patency of the venous pathways, finding baffle leaks, measuring systemic atrioventricular valve regurgitation, or detecting myocardial fibrosis. This review discusses the

various techniques available for CMR imaging in this setting, an approach to obtaining reliable images, strategies and pitfalls to consider, and variations between centers to understand. The goal is to enable providers to obtain a thorough yet efficient study that adequately addresses the patient's clinical needs. © 2014 Elsevier Ireland Ltd.

Broberg, C. S., Mitchell, J., Rehel, S., Grant, A., Gianola, A., Beninato, P., et al. (2015). Electronic medical record integration with a database for adult congenital heart disease: Early experience and progress in automating multicenter data collection. *International Journal of Cardiology, 196*, 178-182.

BACKGROUND: The adoption of electronic health records (EHR) has created an opportunity for multicenter data collection, yet the feasibility and reliability of this methodology is unknown. The aim of this study was to integrate EHR data into a homogeneous central repository specifically addressing the field of adult congenital heart disease (ACHD). METHODS: Target data variables were proposed and prioritized by consensus of investigators at five target ACHD programs. Database analysts determined which variables were available within their institutions' EHR and stratified their accessibility, and results were compared between centers. Data for patients seen in a single calendar year were extracted to a uniform database and subsequently consolidated. RESULTS: From 415 proposed target variables, only 28 were available in discrete formats at all centers. For variables of highest priority, 16/28 (57%) were available at all four sites, but only 11% for those of high priority. Integration was neither simple nor straightforward. Coding schemes in use for congenital heart diagnoses varied and would require additional user input for accurate mapping. There was considerable variability in procedure reporting formats and medication schemes, often with center-specific modifications. Despite the challenges, the final acquisition included limited data on 2161 patients, and allowed for population analysis of race/ethnicity, defect complexity, and body morphometrics. CONCLUSION: Large-scale multicenter automated data acquisition from EHRs is feasible yet challenging. Obstacles stem from variability in data formats, coding schemes, and adoption of non-standard lists within each EHR. The success of large-scale multicenter ACHD research will require institution-specific data integration efforts.

Burch, A. E., Morasco, B. J., & Petry, N. M. (2015). Patients undergoing substance abuse treatment and receiving financial assistance for a physical disability respond well to contingency management treatment. *Journal of Substance Abuse Treatment,*

Physical illness and disability are common in individuals with substance use disorders, but little is known about the impact of physical disability status on substance use treatment outcomes. This study examined the main and interactive effects of physical disability payment status on substance use treatment. Participants (N=1,013) were enrolled in one of six prior randomized clinical trials comparing contingency management (CM) to standard care; 79 (7.8%) participants reported receiving disability payments, CM improved all three primary substance use outcomes: treatment retention, percent negative samples and longest duration of abstinence. There was no significant main effect of physical disability payment status on treatment outcomes; however, a significant treatment condition by physical disability status interaction effect emerged in terms of retention in treatment and duration of abstinence achieved. Patients who were receiving physical disability payments responded particularly well to CM, and their time in treatment and durations of drug and alcohol abstinence increased even more markedly with CM than did that of their counterparts who were not receiving physical disability assistance. These findings suggest an objectively defined cohort of patients receiving substance use treatment who respond particularly well to CM.

Burchiel, K., Liker, M. A., & Lozano, A. M. (2015). Deep brain stimulation: Current assessment, new applications, and future innovations. *Neurosurgical Focus, 38*(6)

Burwick, R. M., Burwick, N., & Feinberg, B. B. (2015). Response: Maternal and cord C5a in response to eculizumab. *Blood, 126*(2), 279-280.

Caetano, R., Kaplan, M. S., Huguet, N., Conner, K., McFarland, B. H., Giesbrecht, N., et al. (2015). Precipitating circumstances of suicide and alcohol intoxication among U.S. ethnic groups. *Alcoholism, Clinical and Experimental Research, 39*(8), 1510-1517.

BACKGROUND: Our goal was to assess the prevalence of 9 different types of precipitating circumstances among suicide decedents, and examine the association between circumstances and postmortem blood alcohol concentration (BAC >/= 0.08 g/dl) across U.S. ethnic groups.

METHODS: Data come from the restricted 2003 to 2011 National Violent Death Reporting System, with postmortem information on 59,384 male and female suicide decedents for 17 U.S. states. RESULTS: Among men, precipitating circumstances statistically associated with a BAC >/= 0.08 g/dl were physical health and job problems for Blacks, and experiencing a crisis, physical health problems, and intimate partner problem for Hispanics. Among women, the only precipitating circumstance associated with a BAC >/= 0.08 g/dl was substance abuse problems other than alcohol for Blacks. The number of precipitating circumstances present before the suicide was negatively associated with a BAC >/= 0.08 g/dl for Whites, Blacks, and Hispanics. CONCLUSIONS: Selected precipitating circumstances were associated with a BAC >/= 0.08 g/dl, and the strongest determinant of this level of alcohol intoxication prior to suicide among all ethnic groups was the presence of an alcohol problem.

Cambareri, G. M., Kovacevic, L., Bayne, A. P., Giel, D., Corbett, S., Schurtz, E., et al. (2015). National multi-institutional cooperative on urolithiasis in children: Age is a significant predictor of urine abnormalities. *Journal of Pediatric Urology,*

INTRODUCTION: Pediatric nephrolithiasis is a growing problem and prior studies have shown the greatest increase in nephrolithiasis in the adolescent population. Metabolic abnormalities have historically been cited as the primary cause of pediatric nephrolithiasis; however, dietary and other factors such as obesity have also been studied with mixed results. OBJECTIVE: We reviewed the charts of pediatric patients with a history of nephrolithiasis to determine the number and types of metabolic abnormalities present on 24-h urine analysis. STUDY DESIGN: We retrospectively reviewed the charts of all pediatric patients with a history of nephrolithiasis from 1999-2013 across four different institutions. The subjects were excluded if they had a history of spina bifida, neurogenic bladder, cerebral palsy, isolated bladder stones, or if they were on medical therapy for nephrolithiasis before the first 24-h urine collection. RESULTS: There were 206 subjects included in the analysis with an average age of 13 (+/-3.9) years. The patients were stratified into two age groups based on an apparent bimodal distribution of metabolic abnormalities, 10 years of age. Metabolic abnormalities were present in 130 children (63.1%) and there was a difference between the groups, with children 10 years of age (75% vs. 60.6%, p = 0.0443) on univariate analysis. In children 10 years hypocitraturia was the most common

disorder present (26.1%). Children 10 years hypocitraturia was the most common disorder present (26.1%). Children 10 years hypocitraturia was the most common disorder present (26.1%). Children 10 years hypocitraturia was the most common disorder present (26.1%). Children 10 years hypocitraturia was the most common disorder present (26.1%). Children 10 years of age were more likely to have low urinary volume. These differences have important implications for future investigative studies on the rising incidence as well as the best course of treatment for children with nephrolithiasis.

Cannon, R. B., Gurgel, R. K., Warren, F. M., & Shelton, C. (2015). Facial nerve outcomes after middle fossa decompression for bell's palsy. *Otology & Neurotology : Official Publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 36*(3), 513-518.

OBJECTIVE: Evaluate the long-term outcomes of facial nerve decompression via the middle fossa approach for Bell's palsy patients with poor prognosis based on clinical and electrodiagnostic testing. STUDY DESIGN: Retrospective case series. SETTING: Tertiary-care, academic medical center. PATIENTS: Fourteen patients underwent surgical decompression for Bell's palsy within 14 days of symptom onset from 2000 to 2012. Surgical criteria included greater than 90% degeneration on ENoG testing and no voluntary EMG potentials. INTERVENTION: Middle cranial fossa (MCF) bony decompression of the facial nerve, including the meatal foramen, labyrinthine segment, and geniculate ganglion. MAIN OUTCOME MEASURES: Long-term facial function, hearing results, and surgical complications. RESULTS: After MCF decompression, 10 patients (71.4%) regained normal or near-normal facial function (House-Brackmann [HB] I or II) within 1 year after surgery, and 5 of those patients (35.7%) improved to HB I. The remaining 4 patients (28.6%) improved to HB III. Patients older than 60 years (n = 3) had an HB III outcome and did significantly worse than the younger-than-60-years group (p = 0.002). The difference in preoperative and postoperative pure tone average and word recognition score was 2.1 dB and 0.9%, respectively. There were no major complications. Minor, transient complications occurred in 22.2% of patients. CONCLUSION: In patients with severe Bell's palsy at risk for a poor facial nerve outcome, MCF decompression of the facial nerve within 14 days of symptom onset provides good facial nerve outcomes with minimal morbidity.

Cassidy, P. B., Honeggar, M., Poerschke, R. L., White, K., Florell, S. R., Andtbacka, R. H., et al.

(2015). The role of thioredoxin reductase 1 in melanoma metabolism and metastasis. *Pigment*

Cell & Melanoma Research,

Although significant progress has been made in targeted and immunologic therapeutics for

melanoma, many tumors fail to respond, and most eventually progress when treated with the

most efficacious targeted combination therapies thus far identified. Therefore, alternative

approaches that exploit distinct melanoma phenotypes are necessary in order to develop new

approaches for therapeutic intervention. Tissue microarrays containing human nevi and

melanomas were used to evaluate levels of the antioxidant protein thioredoxin reductase 1 (TR1),

which was found to increase dramatically as a function of disease progression. Melanoma cell

lines revealed metabolic differences that correlated with TR1 levels. We used this new insight to

design a model treatment strategy that creates a synthetic lethal interaction wherein targeting

TR1sensitizes melanoma to inhibition of glycolytic metabolism, resulting in a dramatic decrease in

metastases in vivo. This approach holds the promise of a new clinical therapeutic strategy,

distinct from oncoprotein inhibition. This article is protected by copyright. All rights reserved.

Cedfeldt, A. S., Bower, E., Flores, C., Brunett, P., Choi, D., & Girard, D. E. (2015). Promoting resident

wellness: Evaluation of a time-off policy to increase residents' utilization of health care services.

Academic Medicine : Journal of the Association of American Medical Colleges, 90(5), 678-683.

PURPOSE: To evaluate awareness and utilization of a new institutional policy to grant residents

time off to access personal and family health care. METHOD: In 2012, two years after policy

implementation, an electronic survey was sent to all 546 residents and fellows at a tertiary care

academic medical center in the United States. Residents were asked questions regarding

awareness of the time-off policy, use of the policy, health care status, reasons for policy use, and

barriers to use. RESULTS: A total of 490 (90%) residents responded. Eighty-nine percent of those

surveyed were aware of the policy. Of those who were aware, 49.7% used the policy to access

health care. Top reasons for policy use were for personal routine or preventive health care, dental

care, and urgent health care needs. The most commonly reported barrier to policy use was

concern about the impact the resident's absence would have on colleagues. CONCLUSIONS:

Implementation of policies to prospectively schedule residents' time off during business hours to

address health care needs is an important means to promote resident wellness. Such policies remove one commonly cited barrier to residents' access to health care. However, residents still reported concerns about impact on peers and patients as the main reason they were reluctant to take the time off to address their health care needs. More work is needed on both wellness policy implementation practices and on refining the systems that will allow seamless and guiltless transitions of care.

Cervera-Juanes, R., Wilhem, L. J., Park, B., Lee, R., Locke, J., Helms, C., et al. (2015). MAOA expression predicts vulnerability for alcohol use. *Molecular Psychiatry,*
The role of the monoamines dopamine (DA) and serotonin (5HT) and the monoamine-metabolizing enzyme monoamine oxidase A (MAOA) have been repeatedly implicated in studies of alcohol use and dependence. Genetic investigations of MAOA have yielded conflicting associations between a common polymorphism (MAOA-LPR) and risk for alcohol abuse. The present study provides direct comparison of tissue-specific MAOA expression and the level of alcohol consumption. We analyzed rhesus macaque MAOA (rhMAOA) expression in blood from males before and after 12 months of alcohol self-administration. In addition, nucleus accumbens core (NAc core) and cerebrospinal fluid (CSF) were collected from alcohol access and control (no alcohol access) subjects at the 12-month time point for comparison. The rhMAOA expression level in the blood of alcohol-naive subjects was negatively correlated with subsequent alcohol consumption level. The mRNA expression was independent of rhMAOA-LPR genotype and global promoter methylation. After 12 months of alcohol use, blood rhMAOA expression had decreased in an alcohol dose-dependent manner. Also after 12 months, rhMAOA expression in the NAc core was significantly lower in the heavy drinkers, as compared with control subjects. The CSF measured higher levels of DA and lower DOPAC/DA ratios among the heavy drinkers at the same time point. These results provide novel evidence that blood MAOA expression predicts alcohol consumption and that heavy alcohol use is linked to low MAOA expression in both the blood and NAc core. Together, the findings suggest a mechanistic link between dampened MAOA expression, elevated DA and alcohol abuse.Molecular Psychiatry advance online publication, 7 July 2015; doi:10.1038/mp.2015.93.

Chalmers, J., Deckert, S., Schmitt, J., & Harmonising Outcome Measures for Atopic Dermatitis (HOME) Initiative Executive Board. (2015). Reaching clinically relevant outcome measures for new pharmacotherapy and immunotherapy of atopic eczema. *Current Opinion in Allergy and Clinical Immunology, 15*(3), 227-233.

PURPOSE OF REVIEW: This article describes the core outcome set (COS) for atopic eczema trials. RECENT FINDINGS: COS describe a minimum set of outcomes to be assessed in a defined situation. COS are required to overcome the current situation of different trials using different endpoints with unclear/insufficient measurement properties resulting in incomparable trials. The global multi-stakeholder Harmonising Outcomes Measures for Eczema initiative developed the Harmonising Outcomes Measures for Eczema roadmap as a generic framework for COS development. Following the establishment of a panel representing all stakeholders, a core set of outcome domains need to be selected based on systematic reviews and consensus methods. Outcome measurement instruments to assess these core domains need to be valid, reliable, and feasible. There is broad global consensus that clinical signs, quality of life, symptoms, and long-term control of flares form the COS for atopic eczema trials. The Eczema Area and Severity Index is recommended to assess clinical signs in atopic eczema trials. Systematic reviews to identify adequate outcome measurement instruments for the other core outcome domains are underway. SUMMARY: Clinical signs should be assessed in all atopic eczema trials by at least the Eczema Area and Severity Index. Quality of life, symptoms, and flares should also be assessed in all atopic eczema trials by a valid, reliable, and feasible instrument.

Chase, J. -. D., & Thiele, D. K. (2015). Continuing the journey: Transitioning to the new tenure-track faculty role. *Western Journal of Nursing Research, 37*(8), 1011-1013.

Chavarha, M., Loney, R. W., Rananavare, S. B., & Hall, S. B. (2015). Hydrophobic surfactant proteins strongly induce negative curvature. *Biophysical Journal, 109*(1), 95-105.

The hydrophobic surfactant proteins SP-B and SP-C greatly accelerate the adsorption of vesicles containing the surfactant lipids to form a film that lowers the surface tension of the air/water interface in the lungs. Pulmonary surfactant enters the interface by a process analogous to the fusion of two vesicles. As with fusion, several factors affect adsorption according to how they

alter the curvature of lipid leaflets, suggesting that adsorption proceeds via a rate-limiting structure with negative curvature, in which the hydrophilic face of the phospholipid leaflets is concave. In the studies reported here, we tested whether the surfactant proteins might promote adsorption by inducing lipids to adopt a more negative curvature, closer to the configuration of the hypothetical intermediate. Our experiments used x-ray diffraction to determine how the proteins in their physiological ratio affect the radius of cylindrical monolayers in the negatively curved, inverse hexagonal phase. With binary mixtures of dioleoylphosphatidylethanolamine (DOPE) and dioleoylphosphatidylcholine (DOPC), the proteins produced a dose-related effect on curvature that depended on the phospholipid composition. With DOPE alone, the proteins produced no change. With an increasing mol fraction of DOPC, the response to the proteins increased, reaching a maximum 50% reduction in cylindrical radius at 5% (w/w) protein. This change represented a doubling of curvature at the outer cylindrical surface. The change in spontaneous curvature, defined at approximately the level of the glycerol group, would be greater. Analysis of the results in terms of a Langmuir model for binding to a surface suggests that the effect of the lipids is consistent with a change in the maximum binding capacity. Our findings show that surfactant proteins can promote negative curvature, and support the possibility that they facilitate adsorption by that mechanism.

Chen, Y., Litvintseva, A. P., Frazzitta, A. E., Haverkamp, M. R., Wang, L., Fang, C., et al. (2015). Comparative analyses of clinical and environmental populations of cryptococcus neoformans in botswana. *Molecular Ecology,*

Cryptococcus neoformans var. grubii (Cng) is the most common cause of fungal meningitis, and its prevalence is highest in sub-Saharan Africa. Patients become infected by inhaling airborne spores or desiccated yeast cells from the environment, where the fungus thrives in avian droppings, trees and soil. To investigate the prevalence and population structure of Cng in southern Africa, we analysed isolates from 77 environmental samples and 64 patients. We detected significant genetic diversity among isolates and strong evidence of geographic structure at the local level. High proportions of isolates with the rare MATa allele were observed in both clinical and environmental isolates; however, the mating-type alleles were unevenly distributed among different subpopulations. Nearly equal proportions of the MATa and MATα mating types

were observed among all clinical isolates and in one environmental subpopulation from the eastern part of Botswana. As previously reported, there was evidence of both clonality and recombination in different geographic areas. These results provide a foundation for subsequent genomewide association studies to identify genes and genotypes linked to pathogenicity in humans. © 2015 The Authors.

Chew, E. Y., Klein, M. L., Clemons, T. E., Agron, E., & Abecasis, G. R. (2015). Author reply. *Ophthalmology, 122*(8), e46-7.

Chiang, J. P., & Trzupek, K. (2015). The current status of molecular diagnosis of inherited retinal dystrophies. *Current Opinion in Ophthalmology, 26*(5), 346-351.
PURPOSE OF REVIEW: We are witnessing lightning-fast advances in the molecular diagnosis of inherited retinal dystrophies, mainly due to the widespread use of next-generation sequencing technologies. The purpose of this review is to highlight the breadth of findings from this in-depth testing approach, and to propose changes to our traditional testing and diagnostic paradigms. Lessons learned from modern molecular testing suggest that the previous concept of inherited retinal dystrophies as a group of 'single gene diseases' may require a significant update. RECENT FINDINGS: All of the known retinal dystrophies genes can now be sequenced. In many cases, this nonhypothesis driven testing strategy is uncovering mutations in unsuspected genes, generating data that challenges established concepts of genetic mechanisms and provides insights regarding genes previously thought to be exclusively related to syndromic disease. Recent advances in testing have improved not only the breadth, but also the depth of genetic data. For example, deep intronic sequencing has uncovered many novel intronic mutations/variations in the ABCA4 gene. SUMMARY: Currently, in approximately 50-60% of patients with nonsyndromic retinal dystrophy, the disease mechanism can be identified. The presence of pathogenic alleles in more than one gene is not uncommon. Retinal dystrophy, with relatively defined clinical presentations and a large but limited number of genes involved, is becoming a model for the next-generation study of molecular disease mechanisms.

Chiang, M. F., Chan, R. V., Vinekar, A., & Woo, R. (2015). Science and art in retinopathy of prematurity diagnosis. *Graefe's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie,*

Choi, D., Wilson, D. J., Grossniklaus, H. E., Harrington, C. A., Dailey, R. A., Ng, J. D., et al. (2015). Fibrosis, gene expression and orbital inflammatory disease. *British Journal of Ophthalmology,* Background/aims To clarify the pathogenesis of fibrosis in inflammatory orbital diseases, we analysed the gene expression in orbital biopsies and compared our results with those reported for idiopathic pulmonary fibrosis. Methods We collected 140 biopsies from 138 patients (58 lacrimal glands; 82 orbital fat). Diagnoses included healthy controls (n=27), non-specific orbital inflammation (NSOI) (n=61), thyroid eye disease (TED) (n=29), sarcoidosis (n=14) and granulomatosis with polyangiitis (GPA) (n=7). Fibrosis was scored on a 0-3 scale by two experts, ophthalmic pathologists. Gene expression was quantified using Affymetrix U133 plus 2.0 microarray. Results Within orbital fat, fibrosis was greatest among subjects with GPA (2.75±0.46) and significantly increased in tissue from subjects with GPA, NSOI or sarcoidosis (p<0.01), but not for TED, compared with healthy controls (1.13±0.69). For lacrimal gland, the average score among controls (1.36±0.48) did not differ statistically from any of the four disease groups. Seventy-three probe sets identified transcripts correlating with fibrosis in orbital fat (false discovery rate <0.05) after accounting for batch effects, disease type, age and sex. Transcripts with increased expression included fibronectin, lumican, thrombospondin and collagen types I and VIII, each of which has been reported upregulated in pulmonary fibrosis. Conclusions A pathologist's recognition of fibrosis in orbital tissue correlates well with increased expression of transcripts that are considered essential in fibrosis. Many transcripts implicated in orbital fibrosis have been previously implicated in pulmonary fibrosis. TED differs from other causes of orbital fat inflammation because fibrosis is not a major component. Marked fibrosis is less common in the lacrimal gland compared with orbital adipose tissue. © 2015 by the BMJ Publishing Group Ltd.

Chung, K. A. (2015). Recognizing and treating neuropsychiatric symptoms in parkinson's disease. *Journal of Clinical Outcomes Management, 22*(7), 323-334.
  • Objective: To review the clinical characteristics, epidemiology, and management of the most

common neuropsychiatric symptoms (NPS) in Parkinson's disease (PD). • Methods: Literature review. • Results: PD has traditionally been considered a disease of impaired motor function. However, neuropsychiatric complications, such as fatigue, depression, anxiety, psychosis, impulse control disorders, and apathy, frequently complicate the course of the illness. Although the development of new medication options in recent years has had a positive benefit on the management of these troublesome symptoms, responses are frequently suboptimal. The development of valid instruments to measure neuropsychiatric symptoms has been vital in research efforts to bridge the gaps in our understanding. Further elucidation of neuropsychiatric pathophysiologies will help to define treatment targets and has the potential to expand our therapeutic armamentarium. • Conclusion: While NPS affect patients with established disease, recent investigations have demonstrated risk of symptoms in those with early untreated stages of PD; therefore, better understanding of NPS should be the goal of practitioners treating the entire continuum of PD. Copyright 2015 by Turner White Communications Inc. All rights reserved.

Clayburgh, D. R., Byrd, J. K., Bonfili, J., & Duvvuri, U. (2015). Intraoperative ultrasonography during transoral robotic surgery. *The Annals of Otology, Rhinology, and Laryngology,*
OBJECTIVE: This study describes the potential application of intraoperative ultrasound imaging during transoral robotic surgery (TORS). METHODS: Ultrasound imaging was performed during transoral robotic resection of oropharyngeal tumors in 10 patients at a tertiary academic center. Ultrasound imaging was utilized to identify large-caliber vessels adjacent to the surgical site. Measurements were also taken on the ultrasound of tumor thickness to determine the deep margin. Following resection, the tumor was sectioned, and a gross measurement of the tumor thickness was obtained. RESULTS: Intraoperative ultrasound use led to the identification of larger-caliber blood vessels within the operative field prior to encountering them visually. Ultrasound could also aid in defining deep tumor margins; the tumor thickness measured via ultrasound was found to be accurate within 1 to 2 mm of the grossly measured tumor thickness. This allowed for focused, careful dissection to protect and avoid blood vessels during dissection as well as improved tumor resection. CONCLUSIONS: The use of intraoperative ultrasound provides additional information to the head and neck surgeon during TORS. This may be used to identify blood vessels and assess tumor margins, thereby improving the safety and efficacy of TORS.

Cleary, D. R., Ozpinar, A., Raslan, A. M., & Ko, A. L. (2015). Deep brain stimulation for psychiatric

disorders: Where we are now. *Neurosurgical Focus, 38*(6)

Fossil records showing trephination in the Stone Age provide evidence that humans have sought

to influence the mind through physical means since before the historical record. Attempts to treat

psychiatric disease via neurosurgical means in the 20th century provided some intriguing initial

results. However, the indiscriminate application of these treatments, lack of rigorous evaluation

of the results, and the side effects of ablative, irreversible procedures resulted in a backlash

against brain surgery for psychiatric disorders that continues to this day. With the advent of

psychotropic medications, interest in invasive procedures for organic brain disease waned.

Diagnosis and classification of psychiatric diseases has improved, due to a better understanding

of psychiatric pathophysiology and the development of disease and treatment biomarkers.

Meanwhile, a significant percentage of patients remain refractory to multiple modes of treatment,

and psychiatric disease remains the number one cause of disability in the world. These data,

along with the safe and efficacious application of deep brain stimulation (DBS) for movement

disorders, in principle a reversible process, is rekindling interest in the surgical treatment of

psychiatric disorders with stimulation of deep brain sites involved in emotional and behavioral

circuitry. This review presents a brief history of psychosurgery and summarizes the development

of DBS for psychiatric disease, reviewing the available evidence for the current application of DBS

for disorders of the mind. © AANS, 2015.

Cook, M. R., Watters, J. M., Barton, J. S., Kamin, C., Brown, S. N., Deveney, K. E., et al. (2015). A

flexible postoperative debriefing process can effectively provide formative resident feedback.

Journal of the American College of Surgeons, 220(5), 959-967.

BACKGROUND: Providing residents with formative operative feedback is one of the ongoing

challenges in modern surgical education. This is highlighted by the recent American Board of

Surgery requirement for formal operative assessments. A flexible and adaptable procedure

feedback process may allow attending surgeons to provide qualitative and quantitative feedback

to residents while encouraging surgeons-in-training to critically reflect on their own performance.

STUDY DESIGN: We designed and implemented a flexible feedback process in which residents

initiated a postoperative feedback discussion and completed a Procedure Feedback Form (PFF)

with their supervising attending surgeon. Comparisons were made between the quantitative and qualitative assessments of attending and resident surgeons. Free text statements describing strengths and weaknesses were analyzed using grounded theory with constant comparison. RESULTS: We identified 346 assessments of 48 surgery residents performing 38 different cases. There was good inter-rater reliability between resident and attending surgeons' quantitative assessment, Goodman and Kruskal gamma > 0.65. Key themes identified on qualitative analysis included flow, technique, synthesis/decision, outcomes, knowledge, and communication/attitudes. Subthematic analysis demonstrated that our novel debriefing procedure was easily adaptable to a wide variety of clinical settings and grew more individualized for senior learners. CONCLUSIONS: This procedure feedback process is easily adaptable to a wide variety of cases and supports resident self-reflection. The process grows in nuance and complexity with the learner and may serve as a guide for a flexible and widely applicable postoperative feedback process.

Corradini, A. (2001). Dynamic time warping for off-line recognition of a small gesture vocabulary. *IEEE ICCV Workshop on Recognition, Analysis, and Tracking of Faces and Gestures in Real-Time Systems, RATFG 2001, , 2001-January.* (January) pp. 82-89.

Considerable effort has been put towards developing intelligent and natural interfaces between users and computer systems. This is done by means of a variety of modes of information (visual, audio, pen, etc.) either used individually or in combination. In this work, we focus on the visual sensory information to recognize human activity inform of hand-arm movements from a small, predefined vocabulary. We accomplish this task by means of a matching technique by determining the distance between the unknown input and a set of previously defined templates. A dynamic time warping (DTW) algorithm is used to perform the time alignment and normalization by computing a temporal transformation allowing the two signals to be matched. The system is trained with finite video sequences of single gesture performances whose start and end point are accurately known. Preliminary experiments are accomplished off-line and result in a recognition accuracy of up to 92%. © 2001 IEEE.

Cotechini, T., Medler, T. R., & Coussens, L. M. (2015). Myeloid cells as targets for therapy in solid tumors. *Cancer Journal (Sudbury, Mass.), 21*(4), 343-350.

It is well established that cancer development ensues based on reciprocal interactions between genomically altered neoplastic cells and diverse populations of recruited "host" cells co-opted to support malignant progression. Among the host cells recruited into tumor microenvironments, several subtypes of myeloid cells, including macrophages, monocytes, dendritic cells, and granulocytes contribute to tumor development by providing tumor-promoting factors as well as a spectrum of molecules that suppress cytotoxic activities of T lymphocytes. Based on compelling preclinical data revealing that inhibition of critical myeloid-based programs leads to tumor suppression, novel immune-based therapies and approaches are now entering the clinic for evaluation. This review discusses mechanisms underlying protumorigenic programming of myeloid cells and discusses how targeting of these has potential to attenuate solid tumor progression via the induction and of mobilization CD8 cytotoxic T cell immunity.

Crawford, J. D., Allan, K. M., Patel, K. U., Hart, K. D., Schreiber, M. A., Azarbal, A. F., et al. (2015). The natural history of indeterminate blunt cerebrovascular injury. *JAMA Surgery,*

Importance: The Denver criteria grade blunt cerebrovascular injuries (BCVIs) but fail to capture many patients with indeterminate findings on initial imaging. Objective: To evaluate outcomes and clinical significance of indeterminate BCVIs (iBCVIs). Design, Setting, and Participants: A retrospective review of all patients treated for BCVIs at our institution from January 1, 2007, through July 31, 2014, was completed. Patients were divided into 2 groups: those with true BCVIs as defined by the Denver criteria and those with iBCVIs, which was any initial imaging suggestive of a cerebrovascular arterial injury not classifiable by the Denver criteria. Main Outcomes and Measures: Primary outcomes were rate of resolution of iBCVIs, freedom from cerebrovascular accident (CVA) or transient ischemic attack (TIA), and 30-day mortality. Results: We identified 100 patients with 138 BCVIs: 79 with true BCVIs and 59 with iBCVIs. With serial imaging, 23 iBCVIs (39.0%) resolved and 21 (35.6%) remained indeterminate, whereas 15 (25.4%) progressed to true BCVI. The rate of CVA or TIA in the iBCVI group was 5.1% compared with 15.2% in the true BCVI group (P = .06). Of the 15 total CVAs or TIAs, 11 (73.3%) resulted from carotid injury and 4 (26.7%) from vertebral artery occlusion (P = .03). By Kaplan-Meier

analysis, there was no difference in freedom from CVA or TIA for the 2 groups (P = .07). Median

clinical follow-up was 91 days. Overall and 30-day mortality for the entire series were 17.4% and

15.2%, respectively. There was no difference in long-term or 30-day mortality between true BCVI

and iBCVI groups. Conclusions and Relevance: Detection of iBCVI has become a common clinical

conundrum with improved and routine imaging. Indeterminate BCVI is not completely benign,

with 25.4% demonstrating anatomical progression to true BCVI and 5.1% developing

cerebrovascular symptoms. We therefore recommend serial imaging and antiplatelet therapy for

iBCVI.

Crawford, L. B., Streblow, D. N., Hakki, M., Nelson, J. A., & Caposio, P. (2015). Humanized mouse

models of human cytomegalovirus infection. *Current Opinion in Virology, 13*, 86-92.
The generation of humanized mouse models in which immune deficient mice are engrafted with

human tissues allows for the direct in vivo investigation of human-restricted viruses. These

humanized mouse models have been developed and improved over the past 30 years. It is now

possible to achieve high levels of human cell engraftment producing human myeloid and

lymphoid lineage cells. Humanized mouse models have been increasingly utilized in the study of

human cytomegalovirus (HCMV), a human-specific beta-herpesvirus that infects myeloprogenitor

cells and establishes a life-long latency in the infected host. This review focuses on the strengths

and limitations of the current humanized mouse models used to study HCMV replication,

pathogenesis and treatment.

Creixell, P., Reimand, J., Haider, S., Wu, G., Shibata, T., Vazquez, M., et al. (2015). Pathway and

network analysis of cancer genomes. *Nature Methods, 12*(7), 615-621.
Genomic information on tumors from 50 cancer types cataloged by the International Cancer

Genome Consortium (ICGC) shows that only a few well-studied driver genes are frequently

mutated, in contrast to many infrequently mutated genes that may also contribute to tumor

biology. Hence there has been large interest in developing pathway and network analysis

methods that group genes and illuminate the processes involved. We provide an overview of

these analysis techniques and show where they guide mechanistic and translational

investigations. © 2015 Nature America, Inc. All rights reserved.

Cservenka, A., Jones, S. A., & Nagel, B. J. (2015). Reduced cerebellar brain activity during reward

processing in adolescent binge drinkers. *Developmental Cognitive Neuroscience,*

Due to ongoing development, adolescence may be a period of heightened vulnerability to the

neurotoxic effects of alcohol. Binge drinking may alter reward-driven behavior and neurocircuitry,

thereby increasing risk for escalating alcohol use. Therefore, we compared reward processing in

adolescents with and without a history of recent binge drinking. At their baseline study visit, all

participants (age=14.86+/-0.88) were free of heavy alcohol use and completed a modified

version of the Wheel of Fortune (WOF) functional magnetic resonance imaging task. Following

this visit, 17 youth reported binge drinking on >/=3 occasions within a 90 day period and were

matched to 17 youth who remained alcohol and substance-naive. All participants repeated the

WOF task during a second visit (age=16.83+/-1.22). No significant effects were found in a region

of interest analysis of the ventral striatum, but whole-brain analyses showed significant group

differences in reward response at the second study visit in the left cerebellum, controlling for

baseline visit brain activity (p/alpha<0.05), which was negatively correlated with mean number

of drinks consumed/drinking day in the last 90 days. These findings suggest that binge drinking

during adolescence may alter brain activity during reward processing in a dose-dependent

manner.

Cservenka, A., Stein, H., Wilson, A. C., & Nagel, B. J. (2015). Neurobiological phenotypes of familial

chronic pain in adolescence: A pilot fMRI study. *The Journal of Pain : Official Journal of the*

American Pain Society,

Parental history of chronic pain has been associated with self-reported pain in child offspring. This

suggests that there may be neurobiological mechanisms associated with pain heritability.

Because emotional circuitry is an important component of pain processing and may also influence

cognition, we used functional magnetic resonance imaging to examine affective processing and

cognitive control using an Emotional Go/NoGo Task in youth with (FH+Pain, N=8) and without

(FH-Pain, N=8) a parental history of chronic pain (mean age = 14.17+/-.34). FH+Pain youth had

widespread reductions in brain activity within limbic and visual processing regions during

processing of positively valenced emotional stimuli, as well as reduced fronto-parietal response

while processing negatively valenced emotional stimuli compared with their peers. Additionally,

during inhibition within a positive emotional context, FH+Pain youth had reduced cognitive control and salience-related brain activity. On the other hand, default mode-related brain response was elevated during inhibitory control within a negative emotional context in these adolescents compared with their peers (p/alpha < 0.05). The current findings indicate differences in both emotional processing and cognitive control brain response in FH+Pain compared with FH-Pain youth, suggesting that both affective and executive functioning pathways may be important markers related to the intergenerational transmission of pain. PERSPECTIVE: This is the first study to examine neurobiological markers of pain risk in adolescents with a family history of chronic pain. These findings may aid in the identification of neural phenotypes related to vulnerability for the onset of pain in at-risk youth.

Cservenka, A., Stroup, M. L., Etkin, A., & Nagel, B. J. (2015). The effects of age, sex, and hormones on emotional conflict-related brain response during adolescence. *Brain and Cognition,*
While cognitive and emotional systems both undergo development during adolescence, few studies have explored top-down inhibitory control brain activity in the context of affective processing, critical to informing adolescent psychopathology. In this study, we used functional magnetic resonance imaging to examine brain response during an Emotional Conflict (EmC) Task across 10-15-year-old youth. During the EmC Task, participants indicated the emotion of facial expressions, while disregarding emotion-congruent and incongruent words printed across the faces. We examined the relationships of age, sex, and gonadal hormones with brain activity on Incongruent vs. Congruent trials. Age was negatively associated with middle frontal gyrus activity, controlling for performance and movement confounds. Sex differences were present in occipital and parietal cortices, and were driven by activation in females, and deactivation in males to Congruent trials. Testosterone was negatively related with frontal and striatal brain response in males, and cerebellar and precuneus response in females. Estradiol was negatively related with fronto-cerebellar, cingulate, and precuneus brain activity in males, and positively related with occipital response in females. To our knowledge, this is the first study reporting the effects of age, sex, and sex steroids during an emotion-cognition task in adolescents. Further research is needed to examine longitudinal development of emotion-cognition interactions and deviations in psychiatric disorders in adolescence.

Danilov, A. V. (2015). Autoimmune haemolytic anaemia occurring during ibrutinib therapy for chronic lymphocytic leukaemia - response to rider et al. *British Journal of Haematology,*

de Godoy Fróes-Salgado, N. R., Gajewski, V., Ornaghi, B. P., Pfeifer, C. S. C., Meier, M. M., Xavier, T. A., et al. (2015). Influence of the base and diluent monomer on network characteristics and mechanical properties of neat resin and composite materials. *Odontology, 103*(2), 160-168. This study evaluated the effect of the combination of two dimethacrylate-based monomers [bisphenol A diglycidyl dimethacrylate (BisGMA) or bisphenol A ethoxylated dimethacrylate (BisEMA)] with diluents either derived from ethylene glycol dimethacrylate (ethylene glycol dimethacrylate, diethylene glycol dimethacrylate, triethylene glycol dimethacrylate, tetraethylene glycol dimethacrylate) or 1,10-decanediol dimethacrylate (D3MA) on network characteristics and mechanical properties of neat resin and composite materials. The degree of conversion, maximum rate of polymerization and water sorption/solubility of unfilled resins and the flexural strength and microhardness of composites (after 24 h storage in water and 3 months storage in a 75 vol% ethanol aqueous solution) were evaluated. Data were analyzed with two-way ANOVA and Tukey's test ($\alpha = 0.05$). The higher conversion and lower water sorption presented by BisEMA co-polymers resulted in greater resistance to degradation in ethanol compared with BisGMA-based materials. In general, conversion and mechanical properties were optimized with the use of long-chain dimethacrylate derivatives of ethylene glycol. D3MA rendered more hydrophobic materials, but with relatively low conversion and mechanical properties. © 2014, The Society of The Nippon Dental University.

de la Cruz, J. S., Sally, M. B., Zatarain, J. R., Crutchfield, M., Ramsey, K., Nielsen, J., et al. (2015). The impact of blood transfusions in deceased organ donors on the outcomes of 1,884 renal grafts from united network for organ sharing region 5. *The Journal of Trauma and Acute Care Surgery,* BACKGROUND: Historically, strategies to reduce acute rejection and improve graft survival in kidney transplant recipients included blood transfusions (BTs) before transplantation. While advents in recipient immunosuppression strategies have replaced this practice, the impact of BTs in the organ donor on recipient graft outcomes has not been evaluated. We hypothesize that BTs in organ donors after neurologic determination of death (DNDDs) translate into improved

recipient renal graft outcomes, as measured by a decrease in delayed graft function (DGF). METHODS: Donor demographics, critical care end points, the use of BTs, and graft outcome data were prospectively collected on DNDDs from March 2012 to October 2013 in the United Network for Organ Sharing Region 5 Donor Management Database. Propensity analysis determined each DNDD's probability of receiving packed red blood cells based on demographic and critical care data as well as provider bias. The primary outcome measure was the rate of DGF (dialysis in the first week after transplantation) in different donor BT groups as follows: no BT, any BT, 1 to 5, 6 to 10, or greater than 10 packed red blood cell units. Regression models determined the relationship between donor BTs and recipient DGF after accounting for known predictors of DGF as well as the propensity to receive a BT. RESULTS: Data were complete for 1,884 renal grafts from 1,006 DNDDs; 52% received any BT, 32% received 1 to 5 U, 11% received 6 to 10, and 9% received greater than 10 U of blood. Grafts from transfused donors had a lower rate of DGF compared with those of the nontransfused donors (26% vs. 34%, $p < 0.001$). After adjusting for known confounders, grafts from donors with any BT had a lower odds of DGF (odds ratio, 0.76; $p = 0.030$), and this effect was greatest in those with greater than 10 U transfused. CONCLUSION: Any BT in a DNDD was associated with a 23% decrease in the odds of recipients developing DGF, and this effect was more pronounced as the number of BTs increased. LEVEL OF EVIDENCE: Prospective observational study, II.

Dean, D., Martinez, M. S., & Newgard, C. D. (2015). Variability in early do not attempt resuscitation orders among patients with serious traumatic brain injury. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine, 22*(1), 54-60.
OBJECTIVES: The objective was describe the use of early do not attempt resuscitation (DNAR) orders in patients with serious traumatic brain injury (TBI) and its association with outcomes. METHODS: This was a retrospective cohort study of all serious TBI patients admitted through the emergency department (ED) to acute care hospitals in California between 2002 and 2010 using ED International Classification of Diseases, 9th revision (ICD-9), admitting diagnosis codes specifying intracranial hemorrhage. DNAR placement within 24 hours of admission was the primary variable of interest. Outcomes included neurosurgical procedures and in-hospital mortality. Hospital and patient characteristics were analyzed using descriptive statistics and

multivariable generalized estimation equation regression models to account for hospital-level

clustering. RESULTS: Of all 76,962 patients with serious TBI, 71,275 were admitted at 141

hospitals that each cared for at least 10 serious TBI patients annually and formed the primary

sample. Early DNAR orders were placed in 7.5% of patients (range = 0 to 36.1% by hospital).

Early DNAR use varied by trauma designation: Level I, 4.0% (95% confidence interval [CI] =

3.8% to 4.4%); Level II, 6.7% (95% CI = 6.5% to 7.1%); Level III, 9.7% (95% CI = 8.4% to

11.3%); and nontrauma hospitals, 10.8% (95% CI = 10.6% to 11.3%). Early DNAR was also

less likely in teaching hospitals (9.3% vs. 4.3%). These results persisted after accounting for

age, year, and hospital-level clustering. In-hospital mortality (39.4% vs. 8.7%) and neurosurgical

interventions (14.5% vs. 19.7%) also differed for patients with versus without early DNAR

orders. Patients 65 years of age and older constituted 87.7% of those with early DNAR orders;

our findings remained qualitatively unchanged when restricted to older adults. CONCLUSIONS:

Use of early DNAR orders among patients with serious TBI is highly variable by individual hospital

and hospital type, suggesting substantial practice variation. Associations with fewer surgical

intervention and higher mortality suggest that such practice variation may be contributing to

differences in TBI outcomes, particularly among older adults.

Del Prete, G., Smedley, J., Macallister, R., Jones, G., Li, B., Hattersley, J., et al. (2015). Comparative

evaluation of co-formulated injectable combination antiretroviral therapy regimens in SIV-

infected rhesus macaques. *AIDS Research and Human Retroviruses,*

The use of non-human primate (NHP) models to study persistent residual virus and viral

eradication strategies in combination antiretroviral therapy (cART) treated individuals requires

regimens that effectively suppress SIV replication to clinically relevant levels in macaques. We

developed and evaluated two novel cART regimens in SIVmac239 infected rhesus macaques: a) a

"triple regimen" containing the nucleo(s/t)ide reverse transcriptase inhibitors emtricitabine (FTC)

and tenofovir disoproxil fumarate (TDF, prodrug of tenofovir [TFV,PMPA]) with the integrase

strand transfer inhibitor dolutegravir (DTG) (n=3), or b) a "quad regimen" containing the same

three drugs plus the protease inhibitor darunavir (DRV) (n=3), with each regimen co-formulated

for convenient administration by a single daily subcutaneous injection. Plasma drug

concentrations were consistent across animals within the triple and quad regimen treated groups,

although DTG levels were lower in the quad regimen animals. Time to achieve plasma viral loads stably <30 viral RNA copies/ml ranged from 12-20 weeks of treatment between animals, and viral loads <30 viral RNA copies/ml plasma were maintained through 40 weeks of follow-up on cART. Notably, although we show virologic suppression and development of viral resistance in a separate cohort of SIV-infected animals treated with oral DRV monotherapy, the addition of DRV in the quad regimen did not confer an apparent virologic benefit during early treatment, hence the quad regimen treated animals were switched to the triple regimen after 4 weeks. This co-formulated triple cART regimen can be safely, conveniently and sustainably administered to durably suppress SIV replication to clinically relevant levels in rhesus macaques.

Delaney, S., Shaffer, B. L., Cheng, Y. W., Vargas, J., Sparks, T. N., Paul, K., et al. (2015). Predictors of cesarean delivery in women undergoing labor induction with a foley balloon. *Journal of Maternal-Fetal and Neonatal Medicine, 28*(9), 1000-1004.

Objective: To examine predictive characteristics for cesarean delivery (CD) in women undergoing labor induction with a Foley balloon (FB). Methods: A secondary analysis of a randomized, double-blind, control trial examining labor induction with a transcervical 30mL or 60mL FB. One-hundred ninety-nine women with term, vertex, singleton pregnancies and Bishop score <5 were randomized to receive a transcervical 30mL or 60mL FB. Mode of delivery, labor complications and neonatal outcomes were recorded. A multivariable model was performed to determine predictive characteristics for CD. Results: Increasing maternal age (p=0.04), nulliparity (p=0.002) and chorioamnionitis (p<0.001) were significantly associated with an elevated risk for CD. Nulliparity was associated in an almost 4-fold increased CD risk (relative risk [RR]: 3.88; 95% confidence interval [CI]: 1.22-12.3). Women aged 40 years, had an almost 3-fold increased risk of CD as compared to women aged 20-29 (RR: 2.91; 95% CI: 1.36-6.19) years. Chorioamnionitis was associated with nearly a 2-fold increased risk for CD (RR: 1.87; 95% CI: 1.06-3.32). A gestational age of 41 weeks, prostaglandin use during induction and induction indication did not affect mode of delivery. Conclusion: In patients undergoing labor induction with a FB, increasing maternal age, nulliparity and chorioamnionitis are associated with an elevated risk for CD. © 2014 Informa UK Ltd. All rights reserved: reproduction in whole or part not permitted.

DeLoughery, T. G. (2015). Anticoagulation considerations for travel to high altitude. *High Altitude Medicine & Biology,*

DeLoughery, Thomas G. Anticoagulation considerations for travel to high altitude. High Alt Med Biol 16:000-000, 2015.-An increasing percentage of the population are on anticoagulation medicine for clinical reasons ranging from stroke prevention in atrial fibrillation to long term prevention of deep venous thrombosis. In recent years, several new direct oral anticoagulants have entered the market. The key questions that should be kept in mind when approaching a potential traveler on anticoagulation are: 1) why is the patient on anticoagulation? 2) do they need to stay on anticoagulation? 3) what are the choices for their anticoagulation? 4) will there be any drug interactions with medications needed for travel? and 5) how will they monitor their anticoagulation while traveling? Knowing the answers to these questions then can allow for proper counseling and planning for the anticoagulated traveler's trip.

Denfeld, Q. E., Mudd, J. O., Gelow, J. M., Chien, C., Hiatt, S. O., & Lee, C. S. (2015). Physical and psychological symptom biomechanics in moderate to advanced heart failure. *Journal of Cardiovascular Nursing, 30*(4), 346-350.

Background: There is a common dissociation between objective measures and patient symptomatology in heart failure (HF). Objective: The aim of this study was to explore the relationship between cardiac biomechanics and physical and psychological symptoms in adults with moderate to advanced HF. Methods: We performed a secondary analysis of data from 2 studies of symptoms among adults with HF. Stepwise regression modeling was performed to examine the influence of cardiac biomechanics (left ventricular internal diastolic diameter, right atrial pressure [RAP], and cardiac index) on symptoms. Results: The average age of the sample (n = 273) was 57 ± 16 years, 61% were men, and 61% had class III or IV HF. Left ventricular internal diastolic diameter (β = 4.22 ± 1.63, P = .011), RAP (β = 0.71 ± 0.28, P = .013), and cardiac index (β = 7.11 ± 3.19, P = .028) were significantly associated with physical symptoms. Left ventricular internal diastolic diameter (β = 0.10 ± 0.05, P = .038) and RAP (β = 0.03 ± 0.01, P = .039) were significantly associated with anxiety. There were no significant biomechanical determinants of depression. Conclusion: Cardiac biomechanics were related to physical symptoms and anxiety, providing preliminary evidence of the biological underpinnings of

symptomatology among adults with HF. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Deveney, K. (2015). Improving american board of surgery in-training examination scores: Motivation matters. *JAMA Surgery,*

DeVoe, J. E., Marino, M., Gold, R., Hoopes, M. J., Cowburn, S., O'Malley, J. P., et al. (2015). Community health center use after oregon's randomized medicaid experiment. *Annals of Family Medicine, 13*(4), 312-320.

PURPOSE: There is debate about whether community health centers (CHCs) will experience increased demand from patients gaining coverage through Affordable Care Act Medicaid expansions. To better understand the effect of new Medicaid coverage on CHC use over time, we studied Oregon's 2008 randomized Medicaid expansion (the "Oregon Experiment"). METHODS: We probabilistically matched demographic data from adults (aged 19-64 years) participating in the Oregon Experiment to electronic health record data from 108 Oregon CHCs within the OCHIN community health information network (originally the Oregon Community Health Information Network) (N = 34,849). We performed intent-to-treat analyses using zero-inflated Poisson regression models to compare 36-month (2008-2011) usage rates among those selected to apply for Medicaid vs not selected, and instrumental variable analyses to estimate the effect of gaining Medicaid coverage on use. Use outcomes included primary care visits, behavioral/mental health visits, laboratory tests, referrals, immunizations, and imaging. RESULTS: The intent-to-treat analyses revealed statistically significant differences in rates of behavioral/mental health visits, referrals, and imaging between patients randomly selected to apply for Medicaid vs those not selected. In instrumental variable analyses, gaining Medicaid coverage significantly increased the rate of primary care visits, laboratory tests, referrals, and imaging; rate ratios ranged from 1.27 (95% CI, 1.05-1.55) for laboratory tests to 1.58 (95% CI, 1.10-2.28) for referrals. CONCLUSIONS: Our results suggest that use of many different types of CHC services will increase as patients gain Medicaid through Affordable Care Act expansions. To maximize access to critical health services, it will be important to ensure that the health care system can support increasing demands by providing more resources to CHCs and other primary care settings.

Dieckmann, N. F., Peters, E., Leon, J., Benavides, M., Baker, D. P., & Norris, A. (2015). The role of
objective numeracy and fluid intelligence in sex-related protective behaviors. *Current HIV Research, 13*(5), 337-346.

A wealth of studies has indicated that greater cognitive ability is related to healthier behaviors
and outcomes throughout the lifespan. In the present paper, we focus on objective numeracy
(ability with numbers) and present findings from a study conducted in the Peruvian Highlands
that examines the relations among formal education, numeracy, other more general cognitive
skills, and a sex-related protective behavior (condom use). Our results show a potential unique
protective effect of numeracy on this healthprotective behavior even after accounting for
measures of fluid intelligence and potential confounding factors. These results add to a growing
literature highlighting the robust protective effect on health behaviors of greater cognitive skills
that are enhanced through schooling. Challenges for future research will be identifying the causal
mechanisms that underlie these effects and translating this knowledge into effective interventions
for improving health.

Dodge, H. H., Zhu, J., Mattek, N., Bowman, M., Ybarra, O., Wild, K., et al. (2015). Web-enabled
conversational interactions as a means to improve cognitive functions: Results of a 6-week
randomized controlled trial. *Alzheimer's & Dementia : Translational Research & Clinical Interventions, 1*(1), 1-12.

INTRODUCTION: Increasing social interaction could be a promising intervention for improving
cognitive function. We examined the feasibility of a randomized controlled trial to assess whether
conversation-based cognitive stimulation, through personal computers, webcams, and a user-
friendly interactive Internet interface had high adherence and a positive effect on cognitive
functions among older adults without dementia. METHODS: Daily 30 minute face-to-face
communications were conducted over a 6-week trial period in the intervention group. The control
group had only a weekly telephone interview. Cognitive status of normal and MCI subjects was
operationally defined as Global Clinical Dementia Rating (CDR) = 0 and 0.5, respectively. Age,
sex, education, Mini-Mental State Exam and CDR score were balancing factors in randomization.
Subjects were recruited using mass-mailing invitations. Pre-post differences in cognitive test
scores and loneliness scores were compared between control and intervention groups using linear

regression models. RESULTS: Eighty-three subjects participated (intervention: n=41, control: n=42). Their mean (std) age was 80.5 (6.8) years. Adherence to the protocol was high; there was no dropout and mean % of days completed out of the targeted trial days among the intervention group was 89% (range: 77%-100%). Among the cognitively intact participants, the intervention group improved more than the control group on a semantic fluency test (p=0.003) at the post-trial assessment and a phonemic fluency test (p=0.004) at the 18th week assessments. Among those with MCI, a trend (p=0.04) of improved psychomotor speed was observed in the intervention group. DISCUSSION: Daily conversations via user-friendly Internet communication programs demonstrated high adherence. Among cognitively intact, the intervention group showed greater improvement in tests of language-based executive functions. Increasing daily social contacts through communication technologies could offer cost-effective home-based preventions. Further studies with a longer duration of follow-up are required to examine whether the intervention slows cognitive declines and delays the onset of dementia.

Doebele, R. C., Davis, L. E., Vaishnavi, A., Le, A. T., Estrada-Bernal, A., Keysar, S., et al. (2015). An oncogenic NTRK fusion in a soft tissue sarcoma patient with response to the tropomyosin-related kinase (TRK) inhibitor LOXO-101. *Cancer Discovery,*

Oncogenic TRK fusions induce cancer cell proliferation and engage critical cancer-related downstream signaling pathways. These TRK fusions occur rarely, but in a diverse spectrum of tumor histologies. LOXO-101 is an orally administered inhibitor of the TRK kinase, and is highly selective only for the TRK family of receptors. Preclinical models of LOXO-101 using TRK-fusion bearing human-derived cancer cell lines demonstrate inhibition of the fusion oncoprotein and cellular proliferation in vitro, and tumor growth in vivo. The tumor of a 41-year old woman with soft tissue sarcoma metastatic to lung was found to harbor an LMNA-NTRK1 gene fusion encoding a functional LMNA-TRKA fusion oncoprotein as determined by an in situ proximity ligation assay. On a phase 1 study of LOXO-101 (ClinicalTrials.gov no. NCT02122913), this patient's tumors underwent rapid and substantial tumor regression, with an accompanying improvement in pulmonary dyspnea, oxygen saturation and plasma tumor markers.

D'Souza, S. L., Anderson, M. A., Korsnes, S. J., Elmunzer, B. J., Piraka, C., Menees, S., et al. (2015). EUS diagnostic criteria for chronic pancreatitis: A comparison of conventional versus rosemont criteria. *Digestive Diseases and Sciences,*

OBJECTIVE: To compare the Rosemont criteria, which are graded features chosen by experts in 2007, versus the conventional criteria, which require >/=3-5 of the 9 features that are "counted as equal," for the diagnosis of chronic pancreatitis by EUS. METHODS: This is a retrospective cohort study. EUS examinations were scored using both criteria, and the following categories compared: 3-CC versus "consistent with" chronic pancreatitis by RC; 3-CC versus "consistent with" and "suggestive of" chronic pancreatitis by RC; 5-CC versus "consistent with" chronic pancreatitis by RC; and 5-CC versus "consistent with" and "suggestive of" chronic pancreatitis by RC. RESULTS: There was a statistically significant difference between 3-CC and RC, either "consistent with" alone or both "consistent with" and "suggestive of" (p < 0.0001). Comparing 5-CC and "consistent with" showed a statistical difference (p = 0.0014), but no difference comparing 5-CC to "consistent with" and "suggestive of." CONCLUSION: CC diagnose more cases of chronic pancreatitis than RC when using 3-CC or when comparing 5-CC to "consistent with" chronic pancreatitis by Rosemont, indicating that the Rosemont criteria are more stringent.

Dueker, J. M., Harrington, R. D., Goldberger, Z. D., Halvorson, S. A., & Nyendak, M. R. (2015). Of mice and men. *Journal of Hospital Medicine,*

Dukes, J. W., Dewland, T. A., Vittinghoff, E., Mandyam, M. C., Heckbert, S. R., Siscovick, D. S., et al. (2015). Ventricular ectopy as a predictor of heart failure and death. *Journal of the American College of Cardiology, 66*(2), 101-109.

BACKGROUND: Studies of patients presenting for catheter ablation suggest that premature ventricular contractions (PVCs) are a modifiable risk factor for congestive heart failure (CHF). The relationship among PVC frequency, incident CHF, and mortality in the general population remains unknown. OBJECTIVES: The goal of this study was to determine whether PVC frequency ascertained using a 24-h Holter monitor is a predictor of a decrease in the left ventricular ejection fraction (LVEF), incident CHF, and death in a population-based cohort. METHODS: We studied 1,139 Cardiovascular Health Study (CHS) participants who were randomly assigned to 24-h

ambulatory electrocardiography (Holter) monitoring and who had a normal LVEF and no history of CHF. PVC frequency was quantified using Holter studies, and LVEF was measured from baseline and 5-year echocardiograms. Participants were followed for incident CHF and death. RESULTS: Those in the upper quartile versus the lowest quartile of PVC frequency had a multivariable-adjusted, 3-fold greater odds of a 5-year decrease in LVEF (odds ratio [OR]: 3.10; 95% confidence interval [CI]: 1.42 to 6.77; p = 0.005), a 48% increased risk of incident CHF (HR: 1.48; 95% CI: 1.08 to 2.04; p = 0.02), and a 31% increased risk of death (HR: 1.31; 95% CI: 1.06 to 1.63; p = 0.01) during a median follow-up of >13 years. Similar statistically significant results were observed for PVCs analyzed as a continuous variable. The specificity for the 15-year risk of CHF exceeded 90% when PVCs included at least 0.7% of ventricular beats. The population-level risk for incident CHF attributed to PVCs was 8.1% (95% CI: 1.2% to 14.9%). CONCLUSIONS: In a population-based sample, a higher frequency of PVCs was associated with a decrease in LVEF, an increase in incident CHF, and increased mortality. Because of the capacity to prevent PVCs through medical or ablation therapy, PVCs may represent a modifiable risk factor for CHF and death.

Dwarkasing, J. T., Marks, D. L., Witkamp, R. F., & van Norren, K. (2015). Hypothalamic inflammation and food intake regulation during chronic illness. *Peptides,*
Anorexia is a common symptom in chronic illness. It contributes to malnutrition and strongly affects survival and quality of life. A common denominator of many chronic diseases is an elevated inflammatory status, which is considered to play a pivotal role in the failure of food-intake regulating systems in the hypothalamus. In this review, we summarize findings on the role of hypothalamic inflammation on food intake regulation involving hypothalamic neuropeptide Y (NPY) and pro-opiomelanocortin (POMC). Furthermore, we outline the role of serotonin in the inability of these peptide based food-intake regulating systems to respond and adapt to changes in energy metabolism during chronic disease.

Eden, K. B., Perrin, N. A., Vesco, K. K., & Guise, J. -. (2014). A randomized comparative trial of two decision tools for pregnant women with prior cesareans. *JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing, 43*(5), 568-579.

Objective: Evaluate tools to help pregnant women with prior cesareans make informed decisions about having trials of labor. Design: Randomized comparative trial. Setting: A research assistant with a laptop met the women in quiet locations at clinics and at health fairs. Participants: Pregnant women (N = 131) who had one prior cesarean and were eligible for vaginal birth after cesarean (VBAC) participated one time between 2005 and 2007. Methods: Women were randomized to receive either an evidence-based, interactive decision aid or two evidence-based educational brochures about cesarean delivery and VBAC. Effect on the decision-making process was assessed before and after the interventions. Results: Compared to baseline, women in both groups felt more informed (F = 23.8, p <.001), were more clear about their birth priorities (F = 9.7, p =.002), felt more supported (F = 9.8, p =.002, and overall reported less conflict (F = 18.1, p < 0.001) after receiving either intervention. Women in their third trimesters reported greater clarity around birth priorities after using the interactive decision aid than women given brochures (F = 9.8, p =.003). Conclusion: Although both decision tools significantly reduced conflict around the birth decision compared to baseline, more work is needed to understand which format, the interactive decision aid or paper brochures, are more effective early and late in pregnancy. © 2014 AWHONN, the Association of Women's Health, Obstetric and Neonatal Nurses.

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

Activation of nuclear beta-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 beta-catenin plays a role in leukemia cell-intrinsic but not -extrinsic BCR-ABL1 kinase-independent TKI resistance. Upon imatinib inhibition of BCR-ABL1 kinase activity, beta-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 beta-catenin expression from BCR-ABL1 kinase activity. In beta-catenin reporter assays, intrinsically resistant cells showed increased transcriptional activity versus parental TKI-sensitive controls, and this was associated with

restored expression of beta-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 beta-catenin levels, arguing against a role for beta-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 beta-catenin contribute to extrinsic, BM-derived TKI resistance. Our data indicate that, while nuclear beta-catenin enhances survival of intrinsically TKI-resistant CML progenitors, it is not required for extrinsic resistance mediated by the BM microenvironment.Leukemia accepted article preview online, 23 July 2015. doi:10.1038/leu.2015.196.

Ellis, L. M., Blanke, C. D., & Roach, N. (2015). Losing "losing the battle with cancer". *JAMA Oncology, 1*(1), 13-14.

Elterman, J., Zonies, D., Stewart, I., Fang, R., & Schreiber, M. (2015). Rhabdomyolysis and acute kidney injury in the injured war fighter. *The Journal of Trauma and Acute Care Surgery,* BACKGROUND: Rhabdomyolysis is a recognized complication of traumatic injury. The correlation of an elevated creatine kinase (CK) level and the development of acute kidney injury (AKI) has been studied in the civilian population. We sought to review the prevalence of rhabdomyolysis in injured war fighters and determine if peak CK levels correlate with AKI. METHODS: This is a retrospective cohort study of patients admitted at a US military treatment facility from January to November 2010. Inclusion criteria were active duty patients transported after explosive, penetrating, or blunt injury. Patients with burns or non-trauma-related admissions were excluded. Rhabdomyolysis was defined as a CK level greater than 5,000 U/L. AKI was defined using the Kidney Disease: Improving Global Outcomes classification. Mann-Whitney U-tests were used to determine the significance for continuous data. Correlations were determined using Spearman's rho. Significance was set at $p < 0.05$. RESULTS: Of the 318 patients included in our analysis, 310 (98%) were male, and the median age was 24 years (21-28 years). Blast was the predominant mechanism of injury (71%), with a median Injury Severity Score (ISS) of 22 (16-29). Rhabdomyolysis developed in 79 patients (24.8%). The median peak CK for all patients was 4,178 U/L and ranged from 208 U/L to 120,000 U/L. Stage 1, 2, and 3 AKI developed in 56

(17.6%), 3 (0.9%), and 7 (2.2%) patients, respectively. There was a weak but statistically significant correlation between peak CK and AKI (r = 0.26, p < 0.05). CONCLUSION: Elevated peak CK levels in the injured war fighter are weakly associated with the development of AKI but are not predictive. The development of clinical practice guidelines would help standardize treatment for rhabdomyolysis in combat casualties and would allow for standardized comparisons in future work. LEVEL OF EVIDENCE: Retrospective study, level III.

Ensrud, K. E., Blackwell, T. L., Cawthon, P. M., Bauer, D. C., Fink, H. A., Schousboe, J. T., et al. (2015). Degree of trauma differs for major osteoporotic fracture events in older men versus older women. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research,*

To examine the degree of trauma in major osteoporotic fractures (MOF) in men versus women, we used data from 15,698 adults aged >/=65 years enrolled in the Osteoporotic Fractures in Men (MrOS) study (5994 men) and the Study of Osteoporotic Fractures (SOF) (9704 women). Participants were contacted tri-annually to ascertain incident fractures, which were confirmed by radiographic reports and coded according to degree of self-reported trauma. Trauma was classified as low (fall from standing height; severe trauma [motor vehicle accident, assault]). MOF included hip, clinical vertebral, wrist, and humerus fractures. Mean fracture follow-up was 9.1 years in SOF and 8.7 years in MrOS. A total of 14.6% of the MOF in men versus 6.3% of the MOF in women were classified as high trauma (p standing height. High-trauma fractures were more significantly common in men versus women at the hip (p = 0.002) and wrist (p < 0.001) but not at the spine or humerus. Among participants with MOF, the odds ratio of a fracture related to high-trauma fracture among men versus women was 3.12 (95% confidence interval [CI] 1.70-5.71) after adjustment for traditional risk factors. Findings were similar in analyses limited to participants with hip fractures (odds ratio [OR] = 3.34, 95% CI 1.04-10.67) and those with wrist fracture (OR = 5.68, 95% CI 2.03-15.85). Among community-dwelling older adults, MOF are more likely to be related to high trauma in men than in women. These findings are not explained by sex differences in conventional risk factors and may reflect a greater propensity among men to engage in risky behavior. (c) 2015 American Society for Bone and Mineral Research.

Eriksson, J. G., Kajantie, E., Thornburg, K., & Osmond, C. (2015). Prenatal and maternal

characteristics and later risk for coronary heart disease among women. *European Journal of

Preventive Cardiology,*

OBJECTIVE: The pace and pathways of early growth have major influences on later health.

Coronary heart disease (CHD) is a major killer and kills more women than men, but usually

manifests about 10 years later in women. Therefore there are fewer studies of early growth and

CHD amongst women than men. METHODS: The Helsinki Birth Cohort Study includes 9817

women born during 1924-1944. We used national registers to identify hospital admissions and

deaths from CHD during 1971-2010. We used a Cox model to obtain hazard ratios (HRs) for CHD.

RESULTS: Altogether 967 women (9.9%) developed CHD. Socioeconomic factors were strongly

and inversely associated with CHD. Neither maternal age nor body mass index (BMI) was

associated with CHD in the daughters. There were inverse associations of birth weight (p = 0.07)

and length (p = 0.02) with CHD in adult life. We divided the mothers according to parity.

Daughters of primiparous women had lower birth weight and shorter birth length than the

offspring of multiparous women (both p-values < 0.001). Birth weight (p = 0.008), birth length

(p = 0.05) and birth BMI (p = 0.02) were all inversely associated with CHD. Among first-born

women, a 1 kg increase in birth weight was associated with a 25% lower risk for CHD (HR 0.75,

95% confidence interval (CI) 0.60-0.93). The findings changed little after adjustment for

socioeconomic factors. Among later-born women none of the birth characteristics was associated

with CHD. CONCLUSIONS: Small birth size is associated with CHD among women. First-born

women with high birth weight appear to be at lower risk for CHD compared with later born

women.

Ethier, C. R., Morrison, J. C., & Clark, A. F. (2015). Introduction to special issue on glaucomatous optic

neuropathy: In vivo models and techniques. *Experimental Eye Research,*

Evans, E., Buonincontri, G., Izquierdo, D., Methner, C., Hawkes, R. C., Ansorge, R. E., et al. (2015).

Combining MRI with PET for partial volume correction improves image-derived input functions in

mice. *IEEE Transactions on Nuclear Science, 62*(3 Pt 1), 628-633.

Accurate kinetic modelling using dynamic PET requires knowledge of the tracer concentration in

plasma, known as the arterial input function (AIF). AIFs are usually determined by invasive blood sampling, but this is prohibitive in murine studies due to low total blood volumes. As a result of the low spatial resolution of PET, image-derived input functions (IDIFs) must be extracted from left ventricular blood pool (LVBP) ROIs of the mouse heart. This is challenging because of partial volume and spillover effects between the LVBP and myocardium, contaminating IDIFs with tissue signal. We have applied the geometric transfer matrix (GTM) method of partial volume correction (PVC) to 12 mice injected with 18F-FDG affected by a Myocardial Infarction (MI), of which 6 were treated with a drug which reduced infarction size [1]. We utilised high resolution MRI to assist in segmenting mouse hearts into 5 classes: LVBP, infarcted myocardium, healthy myocardium, lungs/body and background. The signal contribution from these 5 classes was convolved with the point spread function (PSF) of the Cambridge split magnet PET scanner and a non-linear fit was performed on the 5 measured signal components. The corrected IDIF was taken as the fitted LVBP component. It was found that the GTM PVC method could recover an IDIF with less contamination from spillover than an IDIF extracted from PET data alone. More realistic values of Ki were achieved using GTM IDIFs, which were shown to be significantly different ($p < 0.05$) between the treated and untreated groups.

Faria, V., Erpelding, N., Lebel, A., Johnson, A., Wolff, R., Fair, D., et al. (2015). The migraine brain in transition: Girls versus boys. *Pain,*

The prevalence of migraine has an exponential trajectory that is most obvious in young females between puberty and early adulthood. Adult females are affected twice as much as males. During development, hormonal changes may act on predetermined brain circuits increasing the probability of migraine. However, little is known about the pediatric migraine brain and migraine evolution. Using magnetic resonance imaging (MRI), we evaluated 28 children with migraine (14 females and 14 males) and 28 sex-matched healthy controls to determine differences in brain structure and function between: (a) females and males with migraine, and (b) females and males with migraine during earlier (10-11 years old) vs later (14-16 years) developmental stages compared to matched healthy controls. Compared to males, females had more gray matter (GM) in the primary somatosensory cortex (S1), supplementary motor area (SMA), precuneus (PCu), basal ganglia (BG), and amygdala, as well as greater PCu functional resting state connectivity to

the thalamus, amygdala and BG, and greater amygdala functional resting state connectivity to the thalamus, anterior midcingulate cortex, and SMA. Moreover, older females with migraine had more GM in the S1, amygdala, and caudate compared older males with migraine and matched healthy controls. This is the first study showing sex and developmental differences in pediatric migraineurs in brain regions associated with sensory, motor, and affective functions, providing insight into the neural mechanisms underlying distinct migraine sex phenotypes as well as their evolution that could result in important clinical implications increasing treatment effectiveness.

Ferracane, J. L., & Hilton, T. J. (2015). Polymerization stress - is it clinically meaningful? *Dental Materials : Official Publication of the Academy of Dental Materials,*

OBJECTIVES: The objective of this article is to discuss the evidence for polymerization shrinkage and shrinkage stress of dental composite restoratives in terms of its potential relevance to the clinical situation METHODS: Articles relating to the issue of polymerization contraction stress generation in dental composite materials, and the factors that influence it, were reviewed and included. Particular attention was paid to evidence derived from clinical studies. Articles were identified through PubMed and through the bibliographies of other articles. RESULTS: There is extensive evidence for the presence of polymerization contraction stress in dental composites, as well as evidence for its deleterious effects, which include marginal leakage, gap formation, cuspal deflection, tooth cracking, reduced bond strength and lowered mechanical properties of the restorative. There is little, if any, direct evidence for the clinical effect of these contraction stresses. No study has directly established a link between these stresses and enhanced postoperative sensitivity or recurrent caries, for example. However, the concern over these stresses and the manner in which they influence the placement of current composite materials demonstrates that they are considered to be very important. CONCLUSION: Though no direct evidence exists to prove that the generation of contraction stress in dental composite restorations causes reduced clinical longevity, the indirect evidence from numerous in vitro studies and the concern over controlling their effects proves that they are clinically relevant.

Folmer, R. L., & Theodoroff, S. (2015). Response to: "all treatments in tinnitus are experimental, controversial and futuristic" by de ridder et al (2015). *Journal of the American Academy of Audiology, 26*(7), 678-679.

Folmer, R. L., Theodoroff, S. M., Casiana, L., Shi, Y., Griest, S., & Vachhani, J. (2015). Repetitive transcranial magnetic stimulation treatment for chronic tinnitus: A randomized clinical trial. *JAMA Otolaryngology-- Head & Neck Surgery,*

Importance: Chronic tinnitus negatively affects the quality of life for millions of people. This clinical trial assesses a potential treatment for tinnitus. Objectives: To determine if repetitive transcranial magnetic stimulation (rTMS) can reduce the perception or severity of tinnitus and to test the hypothesis that rTMS will result in a statistically significantly greater percentage of responders to treatment in an active rTMS group compared with a placebo rTMS group. Design, Setting, and Participants: A randomized, participant and clinician or observer-blinded, placebo-controlled clinical trial of rTMS involving individuals who experience chronic tinnitus. Follow-up assessments were conducted at 1, 2, 4, 13, and 26 weeks after the last treatment session. The trial was conducted between April 2011 and December 2014 at Portland Veterans Affairs Medical Center among 348 individuals with chronic tinnitus who were initially screened for participation. Of those, 92 provided informed consent and underwent more detailed assessments. Seventy individuals met criteria for inclusion and were randomized to receive active or placebo rTMS. Sixty-four participants (51 men and 13 women, with a mean [SD] age of 60.6 [8.9] years) were included in the data analyses. No participants withdrew because of adverse effects of rTMS. Interventions: Participants received 2000 pulses per session of active or placebo rTMS at a rate of 1-Hz rTMS daily on 10 consecutive workdays. Main Outcomes and Measures: The Tinnitus Functional Index (TFI) was the main study outcome. Our hypothesis was tested by comparing baseline and posttreatment TFIs for each participant and group. Results: Overall, 18 of 32 participants (56%) in the active rTMS group and 7 of 32 participants (22%) in the placebo rTMS group were responders to rTMS treatment. The difference in the percentage of responders to treatment in each group was statistically significant ($chi2_1$ = 7.94, P < .005). Conclusions and Relevance: Application of 1-Hz rTMS daily for 10 consecutive workdays resulted in a statistically significantly greater percentage of responders to treatment in the active rTMS group compared

with the placebo rTMS group. Improvements in tinnitus severity experienced by responders were

sustained during the 26-week follow-up period. Before this procedure can be implemented

clinically, larger studies should be conducted to refine treatment protocols. Trial Registration:

clinicaltrials.gov Identifier: NCT01104207.

Fornetti, J., Flanders, K. C., Henson, P. M., Tan, A. C., Borges, V. F., & Schedin, P. (2015). Mammary

epithelial cell phagocytosis downstream of TGF-beta3 is characterized by adherens junction

reorganization. *Cell Death and Differentiation,*

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-beta (TGF-beta) signaling is increased during

involution, a pathway known to promote phagocytic capability. To test whether TGF-beta

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-beta3 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 gamma-secretase activity and beta-catenin nuclear

localization. In vitro, pharmacologic inhibitors of gamma-secretase or beta-catenin reduced the

effect of TGF-beta3 on phagocytosis to near baseline levels. However, beta-catenin signaling

through LiCl treatment did not enhance phagocytic capacity, suggesting a model in which both

reorganization of cell junctions and beta-catenin signaling contribute to phagocytosis downstream

of TGF-beta3. 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.Cell Death and Differentiation advance online publication, 26 June 2015; doi:10.1038/cdd.2015.82.

Frontera, J. A., Curtis, J. R., Nelson, J. E., Campbell, M., Gabriel, M., Mosenthal, A. C., et al. (2015). Integrating palliative care into the care of neurocritically ill patients: A report from the improving palliative care in the ICU project advisory board and the center to advance palliative care. *Critical Care Medicine,*

OBJECTIVES: To describe unique features of neurocritical illness that are relevant to provision of high-quality palliative care; to discuss key prognostic aids and their limitations for neurocritical illnesses; to review challenges and strategies for establishing realistic goals of care for patients in the neuro-ICU; and to describe elements of best practice concerning symptom management, limitation of life support, and organ donation for the neurocritically ill. DATA SOURCES: A search of PubMed and MEDLINE was conducted from inception through January 2015 for all English-language articles using the term "palliative care," "supportive care," "end-of-life care," "withdrawal of life-sustaining therapy," "limitation of life support," "prognosis," or "goals of care" together with "neurocritical care," "neurointensive care," "neurological," "stroke," "subarachnoid hemorrhage," "intracerebral hemorrhage," or "brain injury." DATA EXTRACTION AND SYNTHESIS: We reviewed the existing literature on delivery of palliative care in the neurointensive care unit setting, focusing on challenges and strategies for establishing realistic and appropriate goals of care, symptom management, organ donation, and other considerations related to use and limitation of life-sustaining therapies for neurocritically ill patients. Based on review of these articles and the experiences of our interdisciplinary/interprofessional expert advisory board, this report was prepared to guide critical care staff, palliative care specialists, and others who practice in this setting. CONCLUSIONS: Most neurocritically ill patients and their families face the sudden onset of devastating cognitive and functional changes that challenge clinicians to provide patient-centered palliative care within a complex and often uncertain prognostic environment. Application of palliative care principles concerning symptom relief, goal setting, and family emotional support

will provide clinicians a framework to address decision making at a time of crisis that enhances patient/family autonomy and clinician professionalism.

Furlan, A. D., Malmivaara, A., Chou, R., Maher, C. G., Deyo, R. A., Schoene, M., et al. (2015). 2015 updated method guideline for systematic reviews in the cochrane back and neck group. *Spine,*
STUDY DESIGN: Method guideline for systematic reviews of trials of interventions for neck and back pain, and related spinal disordersObjective. To help authors design, conduct and report systematic reviews of trials in this field. SUMMARY OF BACKGROUND DATA: In 1997, the Cochrane Back Review Group editorial board published the Method Guideline for Systematic Reviews, which was updated in 2003 and in 2009. Since then, new methodologic evidence has emerged and standards have changed, therefore it was clear that revisions were needed to the 2009 guideline. In May 2015 the group changed its name to Cochrane Back and Neck (CBN). METHODS: The editorial board met in September 2014 to review the relevant new methodological evidence and determine how it should be incorporated. Members of the advisory board were consulted. Based on the feedback received an updated method guideline was prepared and approved by the editorial board. RESULTS: We have updated recommendations in 7 categories: objectives, literature search, selection criteria, risk of bias assessment, data extraction, data analysis, and reporting of results and conclusions. Each category is classified into minimum criteria (mandatory) and further guidance (optional). This update also includes some new guidance for preparation of summary of finding tables and for conducting non-intervention reviews. CONCLUSION: Citations of previous versions of the method guideline in published scientific articles (1193 in total) suggest that others may find this guideline useful to plan, conduct, or evaluate systematic reviews in the field of back and neck pain, and spinal disorders.

Gadepalli, S. K., Downard, C. D., Thatch, K. A., Islam, S., Azarow, K. S., Chen, M. K., et al. (2015). The effort and outcomes of the pediatric surgery match process: Are we interviewing too many? *Journal of Pediatric Surgery,*
PURPOSE: Increasing numbers of programs participating in the pediatric surgery match has resulted in economic and logistical issues for candidates, General Surgery residencies, and Pediatric Surgery training programs (PSTP). We sought to determine the ideal number of

interviews conducted by programs based on resultant rank order lists (ROL) of matched candidates. METHODS: PSTPs received 4 online surveys regarding interview practices (2011-2012, 2014), and matched candidate ROL (2008-2010, 2012, 2014). Program directors (PD) also provided estimates regarding minimum candidate interview numbers necessary for an effective match (2011-2012, 2014). Kruskal-Wallis equality-of-populations rank tests compared ROL and interview numbers conducted. Quartile regression predicted ROL based on the interview numbers. Wilcoxon signed rank-sum tests compared the interview numbers to the minimal interview number using a matched pair. p Values<0.05 were significant. RESULTS: Survey response rates ranged from 85-100%. Median ROL of matched candidates (2-3.5) did not differ between programs (p=0.09) and the lowest matched ROL for any year was 10-12. Interview numbers did not affect the final candidate ROL (p=0.22). While PDs thought the minimum median interview number should be 20, the number actually conducted was significantly higher (p<0.001). CONCLUSION: These data suggest that PSTPs interview excessive numbers of candidates. Programs and applicants should evaluate mechanisms to reduce interviews to limit costs and effort associated with the match.

Garcia-Aguilar, J., Chow, O. S., Smith, D. D., Marcet, J. E., Cataldo, P. A., Varma, M. G., et al. (2015). Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: A multicentre, phase 2 trial. *The Lancet.Oncology,*
BACKGROUND: Patients with locally advanced rectal cancer who achieve a pathological complete response to neoadjuvant chemoradiation have an improved prognosis. The need for surgery in these patients has been questioned, but the proportion of patients achieving a pathological complete response is small. We aimed to assess whether adding cycles of mFOLFOX6 between chemoradiation and surgery increased the proportion of patients achieving a pathological complete response. METHODS: We did a phase 2, non-randomised trial consisting of four sequential study groups of patients with stage II-III locally advanced rectal cancer at 17 institutions in the USA and Canada. All patients received chemoradiation (fluorouracil 225 mg/m2 per day by continuous infusion throughout radiotherapy, and 45.0 Gy in 25 fractions, 5 days per week for 5 weeks, followed by a minimum boost of 5.4 Gy). Patients in group 1 had total mesorectal excision 6-8 weeks after chemoradiation. Patients in groups 2-4 received two, four, or

six cycles of mFOLFOX6, respectively, between chemoradiation and total mesorectal excision. Each cycle of mFOLFOX6 consisted of racemic leucovorin 200 mg/m2 or 400 mg/m2, according to the discretion of the treating investigator, oxaliplatin 85 mg/m2 in a 2-h infusion, bolus fluorouracil 400 mg/m2 on day 1, and a 46-h infusion of fluorouracil 2400 mg/m2. The primary endpoint was the proportion of patients who achieved a pathological complete response, analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00335816. FINDINGS: Between March 24, 2004, and Nov 16, 2012, 292 patients were registered, 259 of whom (60 in group 1, 67 in group 2, 67 in group 3, and 65 in group 4) met criteria for analysis. 11 (18%, 95% CI 10-30) of 60 patients in group 1, 17 (25%, 16-37) of 67 in group 2, 20 (30%, 19-42) of 67 in group 3, and 25 (38%, 27-51) of 65 in group 4 achieved a pathological complete response (p=0.0036). Study group was independently associated with pathological complete response (group 4 compared with group 1 odds ratio 3.49, 95% CI 1.39-8.75; p=0.011). In group 2, two (3%) of 67 patients had grade 3 adverse events associated with the neoadjuvant administration of mFOLFOX6 and one (1%) had a grade 4 adverse event; in group 3, 12 (18%) of 67 patients had grade 3 adverse events; in group 4, 18 (28%) of 65 patients had grade 3 adverse events and five (8%) had grade 4 adverse events. The most common grade 3 or higher adverse events associated with the neoadjuvant administration of mFOLFOX6 across groups 2-4 were neutropenia (five in group 3 and six in group 4) and lymphopenia (three in group 3 and four in group 4). Across all study groups, 25 grade 3 or worse surgery-related complications occurred (ten in group 1, five in group 2, three in group 3, and seven in group 4); the most common were pelvic abscesses (seven patients) and anastomotic leaks (seven patients). INTERPRETATION: Delivery of mFOLFOX6 after chemoradiation and before total mesorectal excision has the potential to increase the proportion of patients eligible for less invasive treatment strategies; this strategy is being tested in phase 3 clinical trials. FUNDING: National Institutes of Health National Cancer Institute.

Garg, S. K., Lioy, D. T., Knopp, S. J., & Bissonnette, J. M. (2015). Conditional depletion of methyl-CpG-binding protein 2 (MeCP2) in astrocytes depresses the hypercapnic ventilatory response (HCVR) in mice. *Journal of Applied Physiology (Bethesda, Md.: 1985),* , jap.00411.2015. Mice that are deficient in the transcription factor methyl-CpG-binding protein 2 (MeCP2) have a

depressed hypercapnic ventilatory response (HCVR). The expression of MeCP2 can be selectively removed from astrocytes or neurons thus offering a tool to separate the role of this transcription factor in astrocytes from that in neurons. Studies were carried out in the progeny of mice that were a cross between those harboring a tamoxifen (TAM)-inducible cre recombinase transgene driven by the human astrocytic glial fibrillary acidic protein (hGFAP) promoter, or cre recombinase under control of the synapsin promoter, with mice containing a Cre-excisable exon III in the Mecp2 gene. The TAM-conditional excision of the Mecp2 exon allowed respiratory CO2 response to be studied in the same animals before and after selective depletion of MeCP2 in astrocytes. Immunohistochemistry showed that following TAM treatment only ~20% of GFAP labeled cells in the retrotrapazoid nucleus and in the raphe magnus were positive for MeCP2. The slope of the relative increase in minute ventilation as a function of 1,3 and 5% inspired CO2 was depressed in mice with depleted astrocyte MeCP2 compared to wildtype littermates. In contrast, selective depletion in MeCP2 in neurons did not significantly affect slope. While neurons which constitute the respiratory network ultimately determine the ventilatory response to CO2, this study demonstrates that loss of MeCP2 in astrocytes alone is sufficient to result in a dramatic attenuation of the HCVR. We propose that the glial contribution to HCVR is under the control of the MeCP2 gene.

Geltzeiler, C. B., Sims, T. L., & Zigman, A. F. (2015). LAHRI: Laparoscopic-assisted hydrostatic reduction of intussusception. *Journal of Laparoendoscopic & Advanced Surgical Techniques.Part A*,

BACKGROUND/PURPOSE: Intussusception is the most common cause of bowel obstruction in children from 3 months to 3 years of age. In the absence of peritonitis, initial treatment is either hydrostatic or pneumatic reduction. If these measures fail, operative intervention is required. In nonreducible cases, we propose the use of intraoperative hydrostatic enema to achieve or confirm reduction. In this study we describe a cohort of patients who have undergone laparoscopic-assisted hydrostatic reduction of intussusception (LAHRI). MATERIALS AND METHODS: This is a retrospective cohort study of all patients undergoing LAHRI from the years 2011 to 2013. We performed LAHRI in seven children 4 months to 2 years of age. All patients had ileocolic intussusception that failed initial reduction by radiographic enema. With the patient

under general anesthesia, saline enema reduction was facilitated by direct laparoscopic visualization. RESULTS: In 2 of the 7 cases, intussusception reduction was visually confirmed in real time, and only a laparoscopic camera port was required. In 1 patient, the bowel was extensively dilated, requiring mini-laparotomy for visualization. The enema, however, reduced the intussusception without any need for manual reduction. In the remaining 4 cases, minimal laparoscopic manipulation was required after the enema failed to completely reduce the intussusceptum, but enema was used to confirm reduction. No child required bowel resection. CONCLUSIONS: In cases of failed reduction by contrast enema, we have demonstrated LAHRI to be a successful treatment modality. The technique has the advantage of little to no bowel manipulation and has evolved into one performed via a single umbilical port.

Godbersen, J. C., Paiva, C., Danilova, O. V., Berger, A., Brown, J. R., & Danilov, A. V. (2015). Targeting neddylation effectively antagonizes nuclear factor-κB in chronic lymphocytic leukemia B-cells. *Leukemia and Lymphoma, 56*(5), 1566-1569.

Chronic lymphocytic leukemia (CLL) B-cells demonstrate both constitutive and stroma-mediated activation of nuclear factor-κB (NF-κB). NEDD8, a ubiquitin-like protein, regulates activity of Cullin-RING ubiquitin ligases (CRLs) and thus indirectly controls NF-κB activity. Inhibition of CRLs with MLN4924, an investigational agent that targets the NEDD8-activating enzyme, induces accumulation of CRL substrates, including inhibitor of NF-κB (IκB), a negative pathway modulator. We demonstrate that both continuous and pulse treatments with MLN4924 abrogate NF-κB activity in CLL B-cells ex vivo in a CD40L-expressing stromal co-culture system and identify pathways potentially responsible for resistance to MLN4924. To achieve long-lasting therapeutic effects in CLL, combination strategies are likely necessary. © 2015 Informa UK, Ltd.

Goetsch, M. F., Lim, J. Y., & Caughey, A. B. (2015). A practical solution for dyspareunia in breast cancer survivors: A randomized controlled trial. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,*

PURPOSE: Dyspareunia is common in breast cancer survivors because of low estrogen. This study explored whether dyspareunia is introital pain, preventable with analgesic liquid. PATIENTS AND METHODS: In a randomized, controlled, double-blind trial, estrogen-deficient breast cancer

survivors with severe penetrative dyspareunia applied either saline or 4% aqueous lidocaine to the vulvar vestibule for 3 minutes before vaginal penetration. After a 1-month blinded trial of patient-assessed twice-per-week tampon insertion or intercourse, all patients received lidocaine for 2 months in an open-label trial. The primary outcome was patient-related assessment of penetration pain on a scale of zero to 10. Secondary outcomes were sexual distress (Female Sexual Distress Scale), sexual function (Sexual Function Questionnaire), and resumption of intercourse. Comparisons were made with the Mann-Whitney U and Wilcoxon signed rank test with significance set at P 11), and abnormal sexual function. Users of lidocaine reported less pain during intercourse in the blinded phase (median score of 1.0 compared with saline score of 5.3; P = .007). After open-label lidocaine use, 37 (90%) of 41 reported comfortable penetration. Sexual distress decreased (median score, 14; IQR, 3 to 20; P < .001), and sexual function improved in all but one domain. Of 20 prior abstainers from intercourse who completed the study, 17 (85%) had resumed comfortable penetrative intimacy. No partners reported penile numbness. CONCLUSION: Breast cancer survivors with menopausal dyspareunia can have comfortable intercourse after applying liquid lidocaine compresses to the vulvar vestibule before penetration.

Gold, J. A., Stephenson, L. E., Gorsuch, A., Parthasarathy, K., & Mohan, V. (2015). Feasibility of utilizing a commercial eye tracker to assess electronic health record use during patient simulation. *Health Informatics Journal,*

Numerous reports describe unintended consequences of electronic health record implementation. Having previously described physicians' failures to recognize patient safety issues within our electronic health record simulation environment, we now report on our use of eye and screen-tracking technology to understand factors associated with poor error recognition during an intensive care unit-based electronic health record simulation. We linked performance on the simulation to standard eye and screen-tracking readouts including number of fixations, saccades, mouse clicks and screens visited. In addition, we developed an overall Composite Eye Tracking score which measured when, where and how often each safety item was viewed. For 39 participants, the Composite Eye Tracking score correlated with performance on the simulation (p = 0.004). Overall, the improved performance was associated with a pattern of rapid scanning of data manifested by increased number of screens visited (p = 0.001), mouse clicks (p = 0.03) and

saccades (p = 0.004). Eye tracking can be successfully integrated into electronic health record-based simulation and provides a surrogate measure of cognitive decision making and electronic health record usability.

Goldberg, A. B., Fortin, J. A., Drey, E. A., Dean, G., Lichtenberg, E. S., Bednarek, P. H., et al. (2015). Cervical preparation before dilation and evacuation using adjunctive misoprostol or mifepristone compared with overnight osmotic dilators alone: A randomized controlled trial. *Obstetrics and Gynecology,*

OBJECTIVE: To evaluate operative time after adjunctive misoprostol or mifepristone compared with overnight osmotic dilators alone for cervical preparation before dilation and evacuation at 16-23 6/7 weeks of gestation. METHODS: This double-blind, three-arm, multicenter, randomized trial compared overnight osmotic dilators alone, dilators plus 400 micrograms buccal misoprostol 3 hours preoperatively, and dilators plus 200 mg oral mifepristone during dilator placement for dilation and evacuation. Our primary outcome was dilation and evacuation operative time within two cohorts: 16-18 6/7 weeks of gestation (N=150) and 19-23 6/7 weeks of gestation (N=150). Three hundred women were required for 80% power to detect a 2-minute difference in operative time. Secondary outcomes included initial cervical dilation, side effects, physician satisfaction by Likert scale, and complications. RESULTS: Between February 2013 and February 2014 we randomized 300 women evenly across treatment arms. Group demographics were similar. We found no difference in operative time in either gestational cohort (early cohort [minutes]: 5.11+/-3.0 dilators alone, 4.99+/-3.3 misoprostol, 4.33+/-2.0 mifepristone, P=.34; late cohort [minutes]: 7.50+/-3.7 dilators alone, 7.62+/-5.4 misoprostol, 6.74+/-3.2 mifepristone, P=.53). In the early cohort, initial dilation was greater with misoprostol than dilators alone (2.4 compared with 2.0 cm, P=.007). Patients given misoprostol had significantly more pain, fever, and chills. In the late cohort, dilation and evacuation procedures were less difficult after mifepristone (4.1%, 95% confidence interval [CI] 0.0-9.6) than misoprostol (18.8%, 95% CI 7.7-29.8) or dilators alone (18.8%, 95% CI 7.7-29.8; P=.04). We had inadequate power to infer differences in complications: dilators alone (10%, 95% CI 4.2-16.0) compared with misoprostol (2%, 95% CI 0-4.7) compared with mifepristone (2%, 95% CI 0-4.8). CONCLUSION: Despite no difference in operative time, adjunctive mifepristone facilitates later dilation and evacuation compared with

osmotic dilators alone and is better tolerated than misoprostol. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, [www.clinicaltrials.gov,](www.clinicaltrials.gov) NCT01751087. LEVEL OF EVIDENCE: I.

Gonzalez-Castro, J., Petrisor, D., Ballard, D., & Wax, M. K. (2015). The double-barreled radial forearm osteocutaneous free flap. *The Laryngoscope,*
OBJECTIVES/HYPOTHESIS: The radial forearm osteocutaneous free flap (RFOCFF) provides a thin pliable skin paddle with up to 11 cm of bone. A limitation of this flap is the thin bone that is obtained and the lack of suitability for dental implants. A minimum depth of 5 mm and height of 10 mm is required for a bony flap to accept osteointegrated implants. We propose that by double barreling the radial bone, it is possible to reconstruct osseous defects with bone of sufficient caliber to accept dental implants. STUDY DESIGN: Retrospective review of our experience with double-barreled RFOCFF. METHODS: We reviewed all free flaps performed from July 2000 to September 2014 and analyzed patients in whom a radial forearm osteocutaneous flap was used. We then reviewed those who had an osteotomy to form a double-barrel reconstruction. Descriptive data and outcomes were tabulated. RESULTS: A total of 458 osteocutaneous free flaps were performed; 75 were RFOCFF and 18 of these were double barreled. All 18 flaps survived. The reconstructed defect size was between 2.6 and 6.8 cm. One patient had dental implants placed at time of surgery that successfully osteointegrated. Postoperative computed tomography scans were available in nine patients and were used to calculate bone dimensions. Bone depth ranged from 7.91 to 13.22 mm, with a mean of 9.77 +/- 1.53 mm. Bone height ranged from 8.42 to 17.81 mm, with a mean of 13.82 +/- 3.2 mm. CONCLUSIONS: The double-barreled RFOCFF provides dependable long-lasting bone with adequate bone dimensions to support osteointegrated dental implants. LEVEL OF EVIDENCE: 4 Laryngoscope, 2015.

González-Otero, D. M., Alonso, E., Ruiz, J., De Gauna, S. R., Aramendi, E., Ayala, U., et al. (2014). Comparison of time and frequency domain methods for the feedback on chest compression rate. *41st Computing in Cardiology Conference, CinC 2014, , 41.* (January) pp. 1101-1104.
During cardiopulmonary resuscitation feedback systems can help rescuers to achieve optimal chest compression rates. In this paper we describe and compare two methods to provide chest compression rate feedback based only on the thoracic impedance signal, available in automatic

external defibrillators. The first method (time domain) identified the relative maxima of the impedance and characterized each fluctuation by features of amplitude and duration to classify them as compression or non-compression. Then it reported the chest compression rate as the median of the rates of the previous compressions. The frequency domain method computed the Fast Fourier Transform for short windows of the impedance and identified the highest peak in a frequency band. If its amplitude exceeded a dynamic threshold, its frequency was reported as the compression rate. Both methods provided global root mean square errors of the estimated rate below 3.2 min-1 when evaluated with out of hospital cardiac arrest records.

Graff, J. N., & Beer, T. M. (2015). Reducing skeletal-related events in metastatic castration-resistant prostate cancer. *ONCOLOGY (United States), 29*(6)

Groza, T., Kohler, S., Moldenhauer, D., Vasilevsky, N., Baynam, G., Zemojtel, T., et al. (2015). The human phenotype ontology: Semantic unification of common and rare disease. *American Journal of Human Genetics, 97*(1), 111-124.
The Human Phenotype Ontology (HPO) is widely used in the rare disease community for differential diagnostics, phenotype-driven analysis of next-generation sequence-variation data, and translational research, but a comparable resource has not been available for common disease. Here, we have developed a concept-recognition procedure that analyzes the frequencies of HPO disease annotations as identified in over five million PubMed abstracts by employing an iterative procedure to optimize precision and recall of the identified terms. We derived disease models for 3,145 common human diseases comprising a total of 132,006 HPO annotations. The HPO now comprises over 250,000 phenotypic annotations for over 10,000 rare and common diseases and can be used for examining the phenotypic overlap among common diseases that share risk alleles, as well as between Mendelian diseases and common diseases linked by genomic location. The annotations, as well as the HPO itself, are freely available.

Gupta, N., Meraj, R., Tanase, D., James, L. E., Seyama, K., Lynch, D. A., et al. (2015). Accuracy of chest high-resolution computed tomography in diagnosing diffuse cystic lung diseases. *The European Respiratory Journal,*

Hacker, F. M., Whalen, P. S., Lee, V. R., & Caughey, A. B. (2015). Maternal and fetal outcomes of pancreatitis in pregnancy. *American Journal of Obstetrics and Gynecology,*

OBJECTIVE: This study examines maternal and neonatal outcomes associated with pancreatitis in pregnancy, in particular preeclampsia. METHODS: Retrospective cohort study of all singleton non-anomalous pregnancies in California from 2005-2008 with an identification of all cases of pancreatitis. Outcomes of interest included preeclampsia, intrauterine fetal demise, preterm delivery, and neonatal or infant death. Univariate and multivariable analyses were then conducted to examine the association of pancreatitis in pregnancy and maternal characteristics and fetal outcomes. RESULTS: Our cohort of 2,039,870 pregnant women included 342 (0.017%) with pancreatitis. Pancreatitis in pregnancy was not significantly associated with neonatal or infant death. When assessing fetal outcomes, pancreatitis was associated with preterm delivery, small for gestational age, jaundice, respiratory distress syndrome, and intrauterine fetal demise (p<0.001). Of note, pregnancy-associated pancreatitis was found to be associated with preeclampsia and severe preeclampsia in both univariate (p<0.001) and multivariate analysis after controlling for potential confounders (OR 4.21, 95% CI 2.99-5.93; OR 7.85, 95% CI 5.03-12.24). CONCLUSION: We found that pancreatitis in pregnancy was associated with several adverse maternal outcomes; in particular, a strong association existed with preeclampsia, which has its own implications and complications surrounding pregnancy management. Pancreatitis in pregnancy was also associated with increased risk for preterm delivery but not neonatal or infant death, which is consistent with the literature.

Hafren, L., Einarsdottir, E., Kentala, E., Hammaren-Malmi, S., Bhutta, M. F., MacArthur, C. J., et al. (2015). Predisposition to childhood otitis media and genetic polymorphisms within the toll-like receptor 4 (TLR4) locus. *PloS One, 10*(7), e0132551.

BACKGROUND: Predisposition to childhood otitis media (OM) has a strong genetic component, with polymorphisms in innate immunity genes suspected to contribute to risk. Studies on several genes have been conducted, but most associations have failed to replicate in independent cohorts. METHODS: We investigated 53 gene polymorphisms in a Finnish cohort of 624 cases and 778 controls. A positive association signal was followed up in a tagging approach and tested in an independent Finnish cohort of 205 cases, in a British cohort of 1269 trios, as well as in two

cohorts from the United States (US); one with 403 families and the other with 100 cases and 104 controls. RESULTS: In the initial Finnish cohort, the SNP rs5030717 in the TLR4 gene region showed significant association (OR 1.33, P = .003) to OM. Tagging SNP analysis of the gene found rs1329060 (OR 1.33, P = .002) and rs1329057 (OR 1.29, P = .003) also to be associated. In the more severe phenotype the association was stronger. This finding was supported by an independent Finnish case cohort, but the associations failed to replicate in the British and US cohorts. In studies on TLR4 signaling in 20 study subjects, the three-marker risk haplotype correlated with a decreased TNFalpha secretion in myeloid dendritic cells. CONCLUSIONS: The TLR4 gene locus, regulating the innate immune response, influences the genetic predisposition to childhood OM in a subpopulation of patients. Environmental factors likely modulate the genetic components contributing to the risk of OM.

Halliley, J. L., Tipton, C. M., Liesveld, J., Rosenberg, A. F., Darce, J., Gregoretti, I. V., et al. (2015). Long-lived plasma cells are contained within the CD19(-)CD38(hi)CD138(+) subset in human bone marrow. *Immunity, 43*(1), 132-145.

Antibody responses to viral infections are sustained for decades by long-lived plasma cells (LLPCs). However, LLPCs have yet to be characterized in humans. Here we used CD19, CD38, and CD138 to identify four PC subsets in human bone marrow (BM). We found that the CD19(-)CD38(hi)CD138(+) subset was morphologically distinct, differentially expressed PC-associated genes, and exclusively contained PCs specific for viral antigens to which the subjects had not been exposed for more than 40 years. Protein sequences of measles- and mumps-specific circulating antibodies were encoded for by CD19(-)CD38(hi)CD138(+) PCs in the BM. Finally, we found that CD19(-)CD38(hi)CD138(+) PCs had a distinct RNA transcriptome signature and human immunoglobulin heavy chain (VH) repertoire that was relatively uncoupled from other BM PC subsets and probably represents the B cell response's "historical record" of antigenic exposure. Thus, our studies define human LLPCs and provide a mechanism for the life-long maintenance of anti-viral antibodies in the serum.

Hansen, L., Rosenkranz, S. J., Vaccaro, G. M., & Chang, M. F. (2015). Patients with hepatocellular carcinoma near the end of life: A longitudinal qualitative study of their illness experiences. *Cancer*

Nursing, 38(4), E19-E27.

Background: In the United States, the incidence of hepatocellular carcinoma (HCC) is rising. For those diagnosed with terminal HCC, there is no curative treatment and duration of survival is typically 1 to 2 years. Research on illness and treatment experiences toward the end of life for patients with terminal HCC is limited. Objective: The aim of this study was to explore the illness experiences of patients with terminal HCC as they approached the end of life. Methods: This study used a prospective, longitudinal descriptive design. Interview data were collected from 14 patients once a month for up to 6 months, for a total of 45 interviews. Data were analyzed using conventional content analysis. Results: Three major themes (illness perceptions, decision to start treatment, and navigating treatment over time) and 10 subthemes were identified that were reflected across time in all patient experiences. Patients faced challenges with symptom experiences, treatment decisions, and unmet information needs affecting their quality of life. Conclusions: Gaining knowledge about the challenges facing patients with HCC is crucial for designing interventions that optimize their quality of life. Implications for Practice: Healthcare professionals may improve the quality of life of patients with terminal HCC by eliciting patients' perceptions of their illness and treatment decisions, symptom experiences, and information needs as the disease progresses and providing symptom management and offering information tailored to their needs. Care for patients with HCC who are approaching the end of life should be multidisciplinary and include timely referral to palliative care. © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Harry, T., Rahn, D., Semenov, D., Gu, X., Yashar, C., Einck, J., et al. (2015). Cardiac dosimetric evaluation of deep inspiration breath-hold level variances using computed tomography scans generated from deformable image registration displacement vectors. *Medical Dosimetry : Official Journal of the American Association of Medical Dosimetrists,*

There is a reduction in cardiac dose for left-sided breast radiotherapy during treatment with deep inspiration breath-hold (DIBH) when compared with treatment with free breathing (FB). Various levels of DIBH may occur for different treatment fractions. Dosimetric effects due to this and other motions are a major component of uncertainty in radiotherapy in this setting. Recent developments in deformable registration techniques allow displacement vectors between various

temporal and spatial patient representations to be digitally quantified. We propose a method to evaluate the dosimetric effect to the heart from variable reproducibility of DIBH by using deformable registration to create new anatomical computed tomography (CT) scans. From deformable registration, 3-dimensional deformation vectors are generated with FB and DIBH. The obtained deformation vectors are scaled to 75%, 90%, and 110% and are applied to the reference image to create new CT scans at these inspirational levels. The scans are then imported into the treatment planning system and dose calculations are performed. The average mean dose to the heart was 2.5Gy (0.7 to 9.6Gy) at FB, 1.2Gy (0.6 to 3.8Gy, $p < 0.001$) at 75% inspiration, 1.1Gy (0.6 to 3.1Gy, $p = 0.004$) at 90% inspiration, 1.0Gy (0.6 to 3.0Gy) at 100% inspiration or DIBH, and 1.0Gy (0.6 to 2.8Gy, $p = 0.019$) at 110% inspiration. The average mean dose to the left anterior descending artery (LAD) was 19.9Gy (2.4 to 46.4Gy), 8.6Gy (2.0 to 43.8Gy, $p < 0.001$), 7.2Gy (1.9 to 40.1Gy, $p = 0.035$), 6.5Gy (1.8 to 34.7Gy), and 5.3Gy (1.5 to 31.5Gy, $p < 0.001$), correspondingly. This novel method enables numerous anatomical situations to be mimicked and quantifies the dosimetric effect they have on a treatment plan.

Hart, R., Hermsmeyer, J. T., Sethi, R. K., & Norvell, D. C. (2015). Quality and quantity of published studies evaluating lumbar fusion during the past 10 years: A systematic review. *Global Spine Journal, 5*(3), 207-218.

Study Design Systematic review. Clinical Questions (1) Has the proportion and number of randomized controlled trials (RCTs) as an indicator of quality of evidence regarding lumbar fusion increased over the past 10 years? (2) Is there a difference in the proportion of RCTs among the four primary fusion diagnoses (degenerative disk disease, spondylolisthesis, deformity, and adjacent segment disease) over the past 10 years? (3) Is there a difference in the type and quality of clinical outcomes measures reported among RCTs over time? (4) Is there a difference in the type and quality of adverse events measures reported among RCTs over time? (5) Are there changes in fusion surgical approach and techniques over time by diagnosis over the past 10 years? Methods Electronic databases and reference lists of key articles were searched from January 1, 2004, through December 31, 2013, to identify lumbar fusion RCTs. Fusion studies designed specifically to evaluate recombinant human bone morphogenetic protein-2 or other bone substitutes, revision surgery studies, nonrandomized comparison studies, case reports, case

series, and cost-effectiveness studies were excluded. Results Forty-two RCTs between January 1, 2004, and December 31, 2013, met the inclusion criteria and form the basis for this report. There were 35 RCTs identified evaluating patients diagnosed with degenerative disk disease, 4 RCTs evaluating patients diagnosed with degenerative spondylolisthesis, and 3 RCTs evaluating patients with a combination of degenerative disk disease and degenerative spondylolisthesis. No RCTs were identified evaluating patients with deformity or adjacent segment disease. Conclusions This structured review demonstrates that there has been an increase in the available clinical database of RCTs using patient-reported outcomes evaluating the benefit of lumbar spinal fusion for the diagnoses of degenerative disk disease and degenerative spondylolisthesis. Gaps remain in the standardization of reportage of adverse events in such trials, as well as uniformity of surgical approaches used. Finally, continued efforts to develop higher-quality data for other surgical indications for lumbar fusion, most notably in the presence of adult spinal deformity and revision of prior surgical fusions, appear warranted.

Hashem, S. I., Perry, C. N., Bauer, M., Han, S., Clegg, S. D., Ouyang, K., et al. (2015). Brief report: Oxidative stress mediates cardiomyocyte apoptosis in a human model of danon disease and heart failure. *Stem Cells, 33*(7), 2343-2350.

Danon disease is a familial cardiomyopathy associated with impaired autophagy due to mutations in the gene encoding lysosomal-associated membrane protein type 2 (LAMP-2). Emerging evidence has highlighted the importance of autophagy in regulating cardiomyocyte bioenergetics, function, and survival. However, the mechanisms responsible for cellular dysfunction and death in cardiomyocytes with impaired autophagic flux remain unclear. To investigate the molecular mechanisms responsible for Danon disease, we created induced pluripotent stem cells (iPSCs) from two patients with different LAMP-2 mutations. Danon iPSC-derived cardiomyocytes (iPSC-CMs) exhibited impaired autophagic flux and key features of heart failure such as increased cell size, increased expression of natriuretic peptides, and abnormal calcium handling compared to control iPSC-CMs. Additionally, Danon iPSC-CMs demonstrated excessive amounts of mitochondrial oxidative stress and apoptosis. Using the sulfhydryl antioxidant N-acetylcysteine to scavenge free radicals resulted in a significant reduction in apoptotic cell death in Danon iPSC-CMs. In summary, we have modeled Danon disease using human iPSC-CMs from patients with

mutations in LAMP-2, allowing us to gain mechanistic insight into the pathogenesis of this disease. We demonstrate that LAMP-2 deficiency leads to an impairment in autophagic flux, which results in excessive oxidative stress, and subsequent cardiomyocyte apoptosis. Scavenging excessive free radicals with antioxidants may be beneficial for patients with Danon disease. In vivo studies will be necessary to validate this new treatment strategy. Stem Cells 2015;33:2343-2350 © 2015 AlphaMed Press.

Hawkins, S. C., Caudell, M. J., Deloughery, T., & Murray, W. (2014). Activity recommendations for anticoagulated patients may differ, but should be based on accurate data interpretation. *Wilderness & Environmental Medicine, 25*(3), 360-361.

Ho, T., Dukhovny, D., Zupancic, J. A., Goldmann, D. A., Horbar, J. D., & Pursley, D. M. (2015). Choosing wisely in newborn medicine: Five opportunities to increase value. *Pediatrics, 136*(2), e482-9.
BACKGROUND: The use of unnecessary tests and treatments contributes to health care waste. The "Choosing Wisely" campaign charges medical societies with identifying such items. This report describes the identification of 5 tests and treatments in newborn medicine. METHODS: A national survey identified candidate tests and treatments. An expert panel of 51 individuals representing 28 perinatal care organizations narrowed the list over 3 rounds of a modified Delphi process. In the final round, the panel was provided with Grading of Recommendation, Assessment, Development and Evaluation (GRADE) literature summaries of the top 12 tests and treatments. RESULTS: A total of 1648 candidate tests and 1222 treatments were suggested by 1047 survey respondents. After 3 Delphi rounds, the expert panel achieved consensus on the following top 5 items: (1) avoid routine use of antireflux medications for treatment of symptomatic gastroesophageal reflux disease or for treatment of apnea and desaturation in preterm infants, (2) avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection, (3) avoid routine use of pneumograms for predischarge assessment of ongoing and/or prolonged apnea of prematurity, (4) avoid routine daily chest radiographs without an indication for intubated infants, and (5) avoid routine screening term-equivalent or discharge brain MRIs in preterm infants.

CONCLUSIONS: The Choosing Wisely Top Five for newborn medicine highlights tests and treatments that cannot be adequately justified on the basis of efficacy, safety, or cost. This list serves as a starting point for quality improvement efforts to optimize both clinical outcomes and resource utilization in newborn care.

Hoh, B. L., Curran, J., Rokicki, J., Ullman, J. S., Bendok, B. R., Rao, G., et al. (2015). The comparative effectiveness of specific professional educational tools for correcting knowledge gaps among practicing neurosurgeons. *Neurosurgery, 62 Suppl 1*, 133-136.

Holihan, J. L., Alawadi, Z., Martindale, R. G., Roth, J. S., Wray, C. J., Ko, T. C., et al. (2015). Adverse events after ventral hernia repair: The vicious cycle of complications. *Journal of the American College of Surgeons, 221*(2), 478-485.

BACKGROUND: Ventral hernia repairs are one of the most common procedures performed by the general surgeon. They are also among the most complex procedures performed. We hypothesized that with each surgical failure, subsequent ventral hernia repair becomes more complicated and morbid. STUDY DESIGN: We assessed a multicenter database of patients who underwent an elective ventral hernia repair from 2000 to 2012 with at least 6 months of follow-up and elective repairs. Patients were evaluated by the number of previous ventral hernia repairs they had: primary ventral hernia repair (PVHR), first time incisional hernia repair (IHR1), second time incisional hernia repair (IHR2), or third time or greater incisional hernia repair (IHR3). The main outcomes measured were abdominal reoperation, operative duration, surgical site infection (SSI), and hernia recurrence. Complications were assessed and compared between the 4 groups. Time to recurrence was estimated using the Kaplan-Meier curve method by study cohort (PVHR, IHR1, IHR2, IHR3). RESULTS: A total of 794 patients were assessed; of these, 481 (60.6%) had PVHR, 207 (26.1%) had IHR1, 78 (9.8%) had IHR2, and 28 (3.5%) had IHR3. Patients with multiple repairs were more likely to undergo subsequent reoperation, have a longer operative duration, develop SSI, and have a recurrence. At 140 months of follow-up, 37% of primary ventral hernias and 64% of incisional hernias have recurred. The highest recurrence rates are seen in IHR3, with 73% recurring. CONCLUSIONS: Previous ventral hernia repair increases the complication profile of repair, creating a vicious cycle of repair, complications, reoperation, and

re-repair. Furthermore, long-term outcomes for ventral hernia repair are poor. Future studies should focus on hernia prevention and improving long-term outcomes after hernia repair.

Hollander, J. E., & Chang, A. M. (2015). Triple rule out CTA scans or the right test for the right patient. *JACC.Cardiovascular Imaging, 8*(7), 826-827.

Huang, T. -., Cutler, J., Bharne, S., Zhong, J., Weinstock, D., Tyner, J., et al. (2015). Integrated analysis of CRLF2 signaling in acute lymphoblastic leukemia identifies polo-like kinase 1 as a potential therapeutic target. *Leukemia and Lymphoma, 56*(5), 1524-1527.

Hughes, A. J., Hartoonian, N., Parmenter, B., Haselkorn, J. K., Lovera, J. F., Bourdette, D., et al. (2015). Cognitive impairment and community integration outcomes in individuals living with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation,*
OBJECTIVE: To determine the association between unique domains of cognitive impairment and community integration in individuals with multiple sclerosis (MS), and to determine the contributions of cognitive impairment to community integration beyond the influence of demographic and clinical variables. DESIGN: Cross-sectional analysis of objective neuropsychological assessment and self-report data. Data were collected during baseline assessment of a randomized multi-site controlled trial of ginkgo biloba for cognitive impairment in MS. Hierarchical regression analyses examined the association between subjective and objective measures of cognitive impairment and three domains of community integration, adjusting for relevant covariates. SETTING: Two VA medical center MS clinics. PARTICIPANTS: 121 adults (ages 24 to 65) with a confirmed MS diagnosis. INTERVENTIONS: Not applicable. MAIN OUTCOME MEASURES: Primary outcomes were scores on the Home Integration (CIQ-H), Social Integration (CIQ-S), and Productivity (CIQ-P) domains of the Community Integration Questionnaire (CIQ). RESULTS: Cognitive impairment was associated with lower scores on the CIQ-H and CIQ-S, but not the CIQ-P. Greater levels of subjective cognitive impairment were associated with lower scores on the CIQ-H and CIQ-S. Greater levels of objective cognitive impairment, specifically slower processing speed and poorer inhibitory control, were related to lower CIQ-S scores. Subjective and objective measures of cognitive impairment were significantly and independently associated with CIQ-S. CONCLUSIONS: Objective cognitive impairment may interfere with

participation in social activities. Subjective cognitive impairment is also important to assess, because individuals who perceive themselves to be cognitively impaired may be less likely to participate in both home and social activities. Clinical interventions to enhance community integration in individuals with MS may benefit from addressing objective and subjective cognitive impairment by integrating cognitive rehabilitation approaches with self-efficacy-enhancing strategies.

Hunter, J. G., & Deveney, K. E. (2003). Training the rural surgeon: A proposal. *Bulletin of the American College of Surgeons, 88*(5), 13-17.

Ishida, R., Aoki, K., Nakahara, K., Fukuda, Y., Ohori, M., Saito, Y., et al. (2012). *Translin/TRAX deficiency affects mesenchymal differentiation programs and induces bone marrow failure* Springer Netherlands.

The decision regarding self-renewal versus differentiation of hematopoietic stem cells (HSCs) is a crucial issue in bone marrow hematopoiesis. We have generated mice homozygous for an inactivating mutation of the whole Translin gene (Translin-/-) and investigated their hematopoietic status during early and later in life. Here we show that Translin deficiency affects mesenchymal differentiation and results in perturbation of self-renewal HSCs. Young Translin-/- mice, especially around 3 weeks of age, displayed markedly reduced lymphocyte counts in the peripheral blood, attributable to developmental arrest of B-lymphocytes in the earliest progenitor stage. With aging, progressive bone marrow failure was displayed, with developmental arrest of myeloid cells and B lymphocytes in a stroma-dependent manner, and eventually ectopic osteogenesis, vasculogenesis and adipogenesis resulted. Despite apparent hematopoietic aplasia, however, the frequency of HSCs in the bone marrow of mutant mice was remarkably increased. Furthermore, knockdown of Translin and its binding partner protein, TRAX, up-regulated genes associated with mesenchymal differentiation in a mesenchymal stem cell line. Taken together, these findings suggest that the Translin and TRAX complex influences both self-renewal and multilineage differentiation of HSCs by targeting mesenchymal stem/progenitor cells. © 2012 Springer Science+Business Media B.V. All rights reserved.

Jackson, S. L., Abraham, L., Miglioretti, D. L., Buist, D. S., Kerlikowske, K., Onega, T., et al. (2015).

Patient and radiologist characteristics associated with accuracy of two types of diagnostic

mammograms. *AJR.American Journal of Roentgenology, 205*(2), 456-463.

OBJECTIVE: Earlier studies of diagnostic mammography found wide unexplained variability in

accuracy among radiologists. We assessed patient and radiologist characteristics associated with

the interpretive performance of two types of diagnostic mammography. MATERIALS AND

METHODS: Radiologists interpreting mammograms in seven regions of the United States were

invited to participate in a survey that collected information on their demographics, practice

setting, breast imaging experience, and self-reported interpretive volume. Survey data from 244

radiologists were linked to data on 274,401 diagnostic mammograms performed for additional

evaluation of a recent abnormal screening mammogram or to evaluate a breast problem,

between 1998 and 2008. These data were also linked to patients' risk factors and follow-up data

on breast cancer. We measured interpretive performance by false-positive rate, sensitivity, and

AUC. Using logistic regression, we evaluated patient and radiologist characteristics associated

with false-positive rate and sensitivity for each diagnostic mammogram type. RESULTS:

Mammograms performed for additional evaluation of a recent mammogram had an overall false-

positive rate of 11.9%, sensitivity of 90.2%, and AUC of 0.894; examinations done to evaluate a

breast problem had an overall false-positive rate of 7.6%, sensitivity of 83.9%, and AUC of

0.871. Multiple patient characteristics were associated with measures of interpretive

performance, and radiologist academic affiliation was associated with higher sensitivity for both

indications for diagnostic mammograms. CONCLUSION: These results indicate the potential for

improved radiologist training, using evaluation of their own performance relative to best

practices, and for improved clinical outcomes with health care system changes to maximize

access to diagnostic mammography interpretation in academic settings.

Jayaram, H., Strouthidis, N. G., & Kamal, D. S. (2015). Trabeculectomy for normal tension glaucoma:

Outcomes using the moorfields safer surgery technique. *The British Journal of Ophthalmology,*

AIMS: To evaluate long-term outcomes and complications of trabeculectomy for normal tension

glaucoma (NTG) with contemporary surgical techniques. METHODS: Retrospective consecutive,

non-comparative case series of 131 eyes of 98 patients undergoing trabeculectomy between

2007 and 2013 in a dedicated NTG clinic. Data collected during routine clinical care were analysed. Assessment of clinical outcomes included intraocular pressure (IOP) reduction, bleb function, final visual acuity, evidence of glaucoma progression, postoperative complications and further surgical intervention. Surgical failure was defined as a failure to meet specified IOP-related criteria, the need to undergo further glaucoma surgery for raised IOP or loss of light perception vision. A further analysis was also performed which considered failure as glaucoma progression following surgery. Outcomes were evaluated using Kaplan-Meier life-table analysis. RESULTS: The cumulative percentages of unqualified success as defined by a >/=30% reduction of IOP from baseline preoperative maximum (95% CI; IOP of all eyes: mean+/-SD) at 1, 2, 3 and 4 years after surgery were 91.1% (84.1% to 95.1%; 9.7+/-2.9 mm Hg), 74.1% (63.7% to 81.8%; 10.3+/-3.0 mm Hg), 64.8% (52.7% to 74.6%; 10.6+/-2.5 mm Hg) and 62.1% (49.3% to 72.6%; 10.2+/-2.1 mm Hg), respectively. At 2 years of follow-up there was no significant association between either previous cataract surgery or ethnicity and failure. Cumulative percentages of unqualified success at 4 years after surgery as defined by a filtering trabeculectomy bleb or absence of glaucoma progression were 91.6% (83.2% to 95.9%) and 92.3% (81.3% to 97.0%), respectively. Postoperative complications such as early (2.3%) and late (0.8%) hypotony were significantly lower than suggested by the current literature. CONCLUSIONS: Trabeculectomy in NTG patients undertaken using contemporary surgical techniques and intensive postoperative management is associated with more successful long-term outcomes and fewer complications than the currently available literature suggests.

Jensen, J. T. (2015). Nonsurgical permanent contraception for women: Let's complete the job. *Contraception, 92*(2), 89-90.

Johnatty, S., Tyrer, J. P., Kar, S. P., Beesley, J., Lu, Y., Gao, B., et al. (2015). Genome-wide analysis identifies novel loci associated with ovarian cancer outcomes: Findings from the ovarian cancer association consortium. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research,*
PURPOSE: Chemotherapy resistance remains a major challenge in the treatment of ovarian cancer. We hypothesize that germline polymorphisms might be associated with clinical outcome.

EXPERIMENTAL DESIGN: We analyzed ~2.8 million genotyped and imputed SNPs from the iCOGS experiment for progression-free survival (PFS) and overall survival (OS) in 2,901 European epithelial ovarian cancer (EOC) patients who underwent firstline treatment of cytoreductive surgery and chemotherapy regardless of regimen, and in a subset of 1,098 patients treated with >/=4 cycles of paclitaxel and carboplatin at standard doses. We evaluated the top SNPs in 4,434 EOC patients including patients from The Cancer Genome Atlas. Additionally we conducted pathway analysis of all intragenic SNPs and tested their association with PFS and OS using gene set enrichment analysis. RESULTS: Five SNPs were significantly associated (p</=1.0x10-5) with poorer outcomes in at least one of the four analyses, three of which, rs4910232 (11p15.3), rs2549714 (16q23) and rs6674079 (1q22) were located in long non-coding RNAs (lncRNAs) RP11-179A10.1, RP11-314O13.1 and RP11-284F21.8 respectively (p</=7.1x10-6). ENCODE ChIP-seq data at 1q22 for normal ovary shows evidence of histone modification around RP11-284F21.8, and rs6674079 is perfectly correlated with another SNP within the super-enhancer MEF2D, expression levels of which were reportedly associated with prognosis in another solid tumor. YAP1- and WWTR1 (TAZ)-stimulated gene expression, and HDL-mediated lipid transport pathways were associated with PFS and OS, respectively, in the cohort who had standard chemotherapy (pGSEA</=6x10-3). CONCLUSIONS: We have identified SNPs in three lncRNAs that might be important targets for novel EOC therapies.

Jonker, S. S., Louey, S., Giraud, G. D., Thornburg, K. L., & Faber, J. J. (2015). Timing of cardiomyocyte growth, maturation, and attrition in perinatal sheep. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology,*
Studies in altricial rodents attribute dramatic changes in perinatal cardiomyocyte growth, maturation, and attrition to stimuli associated with birth. Our purpose was to determine whether birth is a critical trigger controlling perinatal cardiomyocyte growth, maturation and attrition in a precocial large mammal, sheep (Ovis aries). Hearts from 0-61 d postnatal lambs were dissected or enzymatically dissociated. Cardiomyocytes were measured by micromorphometry, cell cycle activity assessed by immunohistochemistry, and nuclear number counted after DNA staining. Integration of this new data with published fetal data from our laboratory demonstrate that a newly appreciated >30% decrease in myocyte number occurred in the last 10 d of gestation (P <

0.0005) concomitant with an increase in cleaved poly (ADP-ribose) polymerase 1 (P < 0.05), indicative of apoptosis. Bisegmental linear regressions show that most changes in myocyte growth kinetics occur before birth (median = 15.2 d; P < 0.05). Right ventricular but not left ventricular cell number increases in the neonate, by 68% between birth and 60 d postnatal (P = 0.028). We conclude that in sheep few developmental changes in cardiomyocytes result from birth, excepting the different postnatal degrees of free wall hypertrophy between the ventricles. Furthermore, myocyte number is reduced in both ventricles immediately before term, but proliferation increases myocyte number in the neonatal right ventricle.-Jonker, S. S., Louey, S., Giraud, G. D., Thornburg, K. L., Faber, J. J. Timing of cardiomyocyte growth, maturation, and attrition in perinatal sheep.

Kabir, M. M., & Tereshchenko, L. G. (2014). Development of analytical approach for an automated analysis of continuous long-term single lead ECG for diagnosis of paroxysmal atrioventricular block. *41st Computing in Cardiology Conference, CinC 2014, , 41.* (January) pp. 913-916. Reliable detection of significant ECG features such as the P-wave, QRS-complex and T-wave are of major clinical importance, In this paper we introduce a new algorithm based on synchrosqueezing wavelet transform for detection of P-waves in long-term ECG recordings. Synchrosqueezing is a powerful time-frequency analysis tool that provides precise frequency representation of a multicomponent signal through mode decomposition. First, we analyzed four wavelet filters with different filter parameters, to identifY the best specification for quantification of QRS and P-wave. Second, the algorithm was tested on ECG recording comprising of events with paroxysmal atrioventricular block and validated through visual scanning. Using morlet wavelet with a peak frequency of 5Hz and separation of 0.1 Hz, our proposed algorithm was able to detect 95.5% of P-waves. From this study, it appears that synchrosqueezing wavelet transform may provide a powerful robust technique for automated ECG analysis.

Kar, S. P., Tyrer, J. P., Li, Q., Lawrenson, K., Aben, K. K., Anton-Culver, H., et al. (2015). Network-based integration of GWAS and gene expression identifies a HOX-centric network associated with serous ovarian cancer risk. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive*

BACKGROUND: Genome-wide association studies (GWAS) have so far reported 12 loci associated with serous epithelial ovarian cancer (EOC) risk. We hypothesized that some of these loci function through nearby transcription factor (TF) genes and that putative target genes of these TFs as identified by co-expression may also be enriched for additional EOC risk associations. METHODS: We selected TF genes within 1 Mb of the top signal at the 12 genome-wide significant risk loci. Mutual information, a form of correlation, was used to build networks of genes strongly co-expressed with each selected TF gene in the unified microarray data set of 489 serous EOC tumors from The Cancer Genome Atlas. Genes represented in this data set were subsequently ranked using a gene-level test based on results for germline SNPs from a serous EOC GWAS meta-analysis (2,196 cases/4,396 controls). RESULTS: Gene set enrichment analysis identified six networks centered on TF genes (HOXB2, HOXB5, HOXB6, HOXB7 at 17q21.32 and HOXD1, HOXD3 at 2q31) that were significantly enriched for genes from the risk-associated end of the ranked list (P<0.05 and FDR<0.05). These results were replicated (P<0.05) using an independent association study (7,035 cases/21,693 controls). Genes underlying enrichment in the six networks were pooled into a combined network. CONCLUSION: We identified a HOX-centric network associated with serous EOC risk containing several genes with known or emerging roles in serous EOC development. IMPACT: Network analysis integrating large, context-specific data sets has the potential to offer mechanistic insights into cancer susceptibility and prioritize genes for experimental characterization.

Kathpalia, P., Bhatia, A., Robertazzi, S., Ahn, J., Cohen, S. M., Sontag, S., et al. (2015). Indwelling peritoneal catheters in patients with cirrhosis and refractory ascites. *Internal Medicine Journal,*
INTRODUCTION: The prevalence of spontaneous bacterial peritonitis (SBP) in hospitalized cirrhotics with ascites is 10-30%. Treatment for refractory ascites includes paracenteses, TIPS, or drain placement; latter is discouraged due to a perceived infection risk. AIMS: To evaluate the risk of bacterial peritonitis (BP) with peritoneal drains in patients with Child Pugh Class B or C cirrhosis and determine their impact on survival. METHODS: We conducted a retrospective review of end stage liver disease (ESLD) patients with non-malignant, refractory ascites who had peritoneal drains placed for >/= 3 days at Loyola University between 1999-2009. Cell counts

were performed at drain placement and within 72 hours. BP was defined as ascitic PMNs >250/mm3 . Univariate analysis assessed association between demographics, laboratory markers, and development of BP. Kaplan-Meier curve estimates by infection were constructed and survival distributions compared using Log-Rank statistic. RESULTS: There were 227 drain placements during the study period. Twenty-two percent were diagnosed with BP (12% had SBP at drain placement; 10% developed BP within 72 hours). There was no association between BP and baseline characteristics. Patients who developed BP within 72 hours of drain placement had 50% mortality at 5 months compared to 50 months in those without infection (Log-rank p = <0.003). CONCLUSION: In ESLD patients who received an indwelling peritoneal catheter, there was 10% risk of developing BP and significant mortality increase. Though placing drains is not the mainstay of treatment for refractory ascites, we confirm the theoretical adverse risk of peritoneal drains on infection and survival in cirrhotics.

Kim, H., & Jung, J. (2015). New entrants' practice patterns in medicare home health care after the prospective payment system revision in 2008. *Healthcare,*

Background: Medicare home health care spending increased under the prospective payment system (PPS) that was introduced specifically to control the rising spending. To explain this unexpected spending rise, we focused on new home health agencies that entered the market under the PPS. The high profit margins under the PPS attracted many new agencies to the market partially due to home health care's unique feature of low entry costs. We examined whether new entrants were more likely to adopt the practice patterns leading to higher profit margins than incumbent agencies that had been operating in the market before the PPS. Methods: Using 2008 to 2010 Medicare Home Health Claims and Provider of Services File, we estimated regressions of agencies' practice patterns controlling for agency and patient characteristics. Results: We found that new entrants were more likely than incumbents to adopt practice patterns leading to high profit margins. They were more likely to target the 14th and 20th therapy visit where marginal revenue is relatively greater than that of other number of visits. Under the payment system that compensates extra therapy visits but not for other types of visits, entrants were also more likely to provide therapy visits, but less likely to provide medical social service visits. Conclusions: Given the high entry rates of agencies under the PPS,

distinct practice patterns among entrants explain the drastic home health spending increase under the PPS. Heterogeneity in agencies' practice patterns also suggests an opportunity to improve efficiency in the Medicare home health care market. © 2015 Elsevier Inc.

Kiyoshi-Teo, H., & Blegen, M. (2015). Influence of institutional guidelines on oral hygiene practices in intensive care units. *American Journal of Critical Care : An Official Publication, American Association of Critical-Care Nurses, 24*(4), 309-318.

BACKGROUND: Maintaining oral hygiene is a key component of preventing ventilator-associated pneumonia; however, practices are inconsistent. OBJECTIVES: To explore how characteristics of institutional guidelines for oral hygiene influence nurses' oral hygiene practices and perceptions of that practice. METHODS: Oral hygiene section of a larger survey study on prevention of ventilator-associated pneumonia. Critical care nurses at 8 hospitals in Northern California that had more than 1000 ventilator days in 2009 were recruited to participate in the survey. Twenty-one questions addressed oral hygiene practices and practice perceptions. Descriptive statistics, analysis of variance, and Spearman correlations were used for analyses. RESULTS: A total of 576 critical care nurses (45% response rate) responded to the survey. Three types of institutional oral hygiene guidelines existed: nursing policy, order set, and information bulletin. Nursing policy provided the most detail about the oral hygiene care; however, adherence, awareness, and priority level were higher with order sets (P < .05). The content and method of disseminating these guidelines varied, and nursing practices were affected by these differences. Nurses assessed the oral cavity and used oral swabs more often when those practices were included in institutional guidelines. CONCLUSIONS: The content and dissemination method of institutional guidelines on oral hygiene do influence the oral hygiene practices of critical care nurses. Future studies examining how institutional guidelines could best be incorporated into routine workflow are needed.

Klingensmith, M. E., Awad, M., Delman, K. A., Deveney, K., Fahey, T. J.,3rd, Lees, J. S., et al. (2015). Early results from the flexibility in surgical training research consortium: Resident and program director attitudes toward flexible rotations in senior residency. *Journal of Surgical Education,*

OBJECTIVE: To assess the attitudes of residents and program directors (PDs) involved in flexible

training to gauge satisfaction with this training paradigm and elicit limitations. DESIGN: Anonymous surveys were sent to residents and PDs in participant programs. Respondents were asked to rate responses on a 5-point Likert scale (1 = strongly disagree and 5 = strongly agree). SETTING: A total of 9 residency programs that are collaborating to prospectively study the effect of flexible tracks on resident performance and outcome. PARTICIPANTS: A total of 138 residents who were in clinical years 4 and 5 and 10 PDs. RESULTS: Of the 138 possible residents, 100 responded to the resident survey (72.5% response rate). Among resident respondents, 33% were participating in a flexible track option. The most frequently listed specialties of focus were cardiothoracic surgery (19%), vascular surgery (13%), acute care surgery (11%), colorectal surgery (8%), surgical oncology (7%), and pediatric surgery (7%). Participants in flexible tracks tended to strongly agree that their career would be enhanced by flexible rotations; interestingly, of those not in flexible tracks, most tended to also agree that flexible rotations would enhance their future careers. Flexible track participants report receiving greater autonomy on flexible rotations and believe they would be better prepared for fellowship and career. They express overall very high satisfaction with the flexible experience. Limitations expressed by residents (in flexible tracks or not) include uncertainty for how this paradigm serves those interested in comprehensive general surgery, concern about scheduling difficulties, and some displeasure in missing high-volume general surgery rotations in lieu of specialty-focused rotations. The PD survey was completed by 8 of 9 PDs for a response rate of 89%. All the respondents agreed or strongly agreed that careers of residents are enhanced by flexible rotations and that important operative and clinical experiences are gained. Overall, 87.5% of PD respondents agreed or strongly agreed that those in flexible tracks have greater opportunities for mentorship in their chosen field. PDs also expressed high levels of satisfaction with flexible rotations. Limitations include concerns that the flexibility option presents scheduling difficulties and does not go far enough in reforming postgraduate education. CONCLUSIONS: This survey of 9 residency programs participating in flexible tracks indicates satisfaction with this training option. The role of comprehensive general surgery as a training end point and scheduling difficulties remain as major challenges. Outcomes of graduates in these tracks and control peers are being prospectively evaluated.

Korkola, J. E., Collisson, E. A., Heiser, L., Oates, C., Bayani, N., Itani, S., et al. (2015). Decoupling of

the PI3K pathway via mutation necessitates combinatorial treatment in HER2+ breast cancer.

PloS One, 10(7), e0133219.

We report here on experimental and theoretical efforts to determine how best to combine drugs

that inhibit HER2 and AKT in HER2+ breast cancers. We accomplished this by measuring cellular

and molecular responses to lapatinib and the AKT inhibitors (AKTi) GSK690693 and GSK2141795

in a panel of 22 HER2+ breast cancer cell lines carrying wild type or mutant PIK3CA. We

observed that combinations of lapatinib plus AKTi were synergistic in HER2+/PIK3CAmut cell lines

but not in HER2+/PIK3CAwt cell lines. We measured changes in phospho-protein levels in 15 cell

lines after treatment with lapatinib, AKTi or lapatinib + AKTi to shed light on the underlying

signaling dynamics. This revealed that p-S6RP levels were less well attenuated by lapatinib in

HER2+/PIK3CAmut cells compared to HER2+/PIK3CAwt cells and that lapatinib + AKTi reduced

p-S6RP levels to those achieved in HER2+/PIK3CAwt cells with lapatinib alone. We also found

that that compensatory up-regulation of p-HER3 and p-HER2 is blunted in PIK3CAmut cells

following lapatinib + AKTi treatment. Responses of HER2+ SKBR3 cells transfected with

lentiviruses carrying control or PIK3CAmut sequences were similar to those observed in

HER2+/PIK3CAmut cell lines but not in HER2+/PIK3CAwt cell lines. We used a nonlinear ordinary

differential equation model to support the idea that PIK3CA mutations act as downstream

activators of AKT that blunt lapatinib inhibition of downstream AKT signaling and that the effects

of PIK3CA mutations can be countered by combining lapatinib with an AKTi. This combination

does not confer substantial benefit beyond lapatinib in HER2+/PIK3CAwt cells.

Ku, J. H., Danve, A., Pang, H., Choi, D., & Rosenbaum, J. T. (2015). Determinants of patient

satisfaction in an academic rheumatology practice. *Journal of Clinical Rheumatology : Practical

Reports on Rheumatic & Musculoskeletal Diseases, 21*(5), 256-262.

BACKGROUND: Although patient satisfaction is used as a measure of physician performance and

is an essential component of chronic disease management, there is limited understanding about

factors affecting satisfaction in rheumatologic settings. OBJECTIVE: Our study aimed to identify

factors affecting satisfaction in outpatients with rheumatic diseases by correlating satisfaction

with various factors. METHODS: We conducted a cross-sectional cohort study of rheumatology

patients at Oregon Health & Science University in 2013. Patient satisfaction ratings were obtained, and data were collected from medical records. Descriptive and quantile regression analyses were performed to describe the population and to model predictors of satisfaction. RESULTS: We obtained data from 573 patients, 76% were females, 92% were non-Hispanic white, with a mean age of 50 (SD, 15) years. Female gender (beta = 7.51; 95% confidence interval [CI], 6.16-8.86), older age (beta = 0.10; 95% CI, 0.01-0.20), and follow-up visit (beta = 4.04; 95% CI, 0.14-7.93) had a positive impact on satisfaction, whereas polymyalgia rheumatica (beta = -9.25; 95% CI, -15.25 to -3.25), arthralgia (beta = -8.67; 95% CI, -16.60 to -0.74), myalgia (beta = -8.67; 95% CI, -16.60 to -0.74), gout (beta = -7.5; 95% CI, -14.13 to -0.89), ankylosing spondylitis (beta = -5.20; 95% CI, -9.65 to -0.75), pain (beta = -4.62; 95% CI, -8.43 to -0.81), fibromyalgia (beta = -4.62; 95% CI, -7.80 to -1.44), longer visit duration (beta = -0.08; 95% CI, -0.13 to -0.03), and afternoon appointments (beta = -4.62; 95% CI, -7.04 to -2.20) had an inverse effect. CONCLUSIONS: Factors contributing to satisfaction scores differed for median satisfaction level and lower satisfaction level. Most of the factors identified as influencing patient satisfaction were unrelated to the physician or the skills of that physician.

Lahvis, G. P., Panksepp, J. B., Kennedy, B. C., Wilson, C. R., & Merriman, D. K. (2015). Social conditioned place preference in the captive ground squirrel (ictidomys tridecemlineatus): Social reward as a natural phenotype. *Journal of Comparative Psychology (Washington, D.C.: 1983), 129*(3), 291-303.

Social behaviors of wild animals are often considered within an ultimate framework of adaptive benefits versus survival risks. By contrast, studies of laboratory animals more typically focus on affective aspects of behavioral decisions, whether a rodent derives a rewarding experience from social encounter, and how this experience might be initiated and maintained by neural circuits. Artificial selection and inbreeding have rendered laboratory animals more affiliative and less aggressive than their wild conspecifics, leaving open the possibility that social reward is an artifact of domestication. We compared social behaviors of wild and captive population of juvenile 13-lined ground squirrels (Ictidomys tridecemlineatus), the latter being 2nd- and 3rd-generation descendants of wild individuals. At an age corresponding to emergence from the burrow, postnatal day (PD) 38, captive squirrels engaged in vigorous social approach and play and these

juvenile behaviors declined significantly by PD 56. Similarly, young wild squirrels expressed social proximity and play; affiliative interactions declined with summer's progression and were replaced by agonistic chasing behaviors. Social conditioned place preference testing (conditioned PDs 40-50) indicated that adolescent squirrels derived a rewarding experience from social reunion. Our results support the contention that undomesticated rodents have the capacity for social reward and more generally suggest the possibility that positive affective experiences may support group cohesion, social cooperation, and altruism in the wild. (PsycINFO Database Record

Lal, S., Kersch, C., Beeson, K. A., Wu, Y. J., Muldoon, L. L., & Neuwelt, E. A. (2015). Interactions between alphav-integrin and HER2 and their role in the invasive phenotype of breast cancer cells in vitro and in rat brain. *PloS One, 10*(7), e0131842.

BACKGROUND: We tested the hypothesis that alphav-integrin and the human epidermal growth factor receptor type 2 (HER2) interact with each other in brain trophic metastatic breast cancer cells and influence their invasive phenotype. METHODS: Clones of MDA-MB231BR human breast cancer cells with stable knock down of alphav-integrin in combination with high or low levels of HER2 were created. The interactions of these two proteins and their combined effect on cell migration and invasion were investigated in vitro and in vivo. RESULTS: Knockdown of alphav-integrin in MDA-MB231BR clones altered the actin cytoskeleton and cell morphology. HER2 co-precipitated with alphav-integrin in three breast cancer cell lines in vitro, suggesting they complex in cells. Knockdown of alphav-integrin altered HER2 localization from its normal membrane position to a predominantly lysosomal localization. When alphav-integrin expression was decreased by 69-93% in HER2-expressing cells, cellular motility was significantly reduced. Deficiency of both alphav-integrin and HER2 decreased cellular migration and invasion by almost 90% compared to cells expressing both proteins (P<0.01). After intracerebral inoculation, cells expressing high levels of both alphav-integrin and HER2 showed a diffusely infiltrative tumor phenotype, while cells deficient in alphav-integrin and/or HER2 showed a compact tumor growth phenotype. In the alphav-integrin positive/HER2 positive tumors, infiltrative growth was 57.2 +/- 19% of tumor volume, compared to only 5.8 +/- 6.1% infiltration in the double deficient tumor cells. CONCLUSIONS: alphav-integrin interacts with HER2 in breast cancer cells and may regulate HER2 localization. The combined impacts of alphav-integrin and HER2 influence the invasive

phenotype of breast cancer cells. Targeting alphav-integrin in HER2-positive breast cancer may slow growth and decrease infiltration in the normal brain.

Lampi, K. J., Murray, M. R., Peterson, M. P., Eng, B. S., Yue, E., Clark, A. R., et al. (2015). Differences in solution dynamics between lens beta-crystallin homodimers and heterodimers probed by hydrogen-deuterium exchange and deamidation. *Biochimica Et Biophysica Acta,*
BACKGROUND: Lens transparency is due to the ordered arrangement of the major structural proteins, called crystallins. betaB2 crystallin in the lens of the eye readily forms dimers with other beta-crystallin subunits, but the resulting heterodimer structures are not known and were investigated in this study. METHODS: Structures of betaA3 and betaB2 crystallin homodimers and the betaA3/betaB2 crystallin heterodimers were probed by measuring changes in solvent accessibility using hydrogen-deuterium exchange with mass spectrometry. We further mimicked deamidation in betaB2 and probed the effect on the betaA3/betaB2 heterodimer. Results were confirmed with chemical crosslinking and NMR. RESULTS: Both betaA3 and betaB2 had significantly decreased deuterium levels in the heterodimer compared to their respective homodimers, suggesting that they had less solvent accessibility and were more compact in the heterodimer. The compact structure of betaB2 was supported by the identification of chemical crosslinks between lysines in betaB2 within the heterodimer that were inconsistent with betaB2's extended homodimeric structure. The compact structure of betaA3 was supported by an overall decrease in mobility of betaA3 in the heterodimer detected by NMR. In betaB2, peptides 70-84 and 121-134 were exposed in the homodimer, but buried in the heterodimer with >/=50% decreases in deuterium levels. Homologous peptides in betaA3, 97-109 and 134-149, had 25-50% decreases in deuterium levels in the heterodimer. These peptides are probable sites of interaction between betaB2 and betaA3 and are located at the predicted interface between subunits with bent linkers. Deamidation at Q184 in betaB2 at this predicted interface led to a less compact betaB2 in the heterodimer. The more compact structure of the betaA3/betaB2 heterodimer was also more heat stable than either of the homodimers. CONCLUSIONS: The major structural proteins in the lens, the beta-crystallins, are not static, but dynamic in solution, with differences in accessibility between the homo-and hetero-dimers. This structural flexibility, particularly of betaB2, may facilitate formation of different size higher-ordered structures found

in the transparent lens. GENERAL SIGNIFICANCE: Understanding complex hetero-oligomer interactions between beta-crystallins in normal lens and how these interactions change during aging is fundamental to understanding the cause of cataracts.

Lange, D., Corbett, J., Lippke, S., Knoll, N., & Schwarzer, R. (2015). The interplay of intention, autonomy, and sex with dietary planning: A conditional process model to predict fruit and vegetable intake. *British Journal of Health Psychology,*
OBJECTIVES: Dietary intentions are supposed to engender planning processes, which in turn stimulate dietary behaviour change. However, some studies failed to find such mediation effects, which suggest more complex and not yet unravelled relationships between these factors. One explanation may be that mediation works better under certain circumstances or only for specific subgroups. This study addresses this reasoning by examining autonomy beliefs and sex as putative moderators of the hypothesized mediation chain. DESIGN AND METHODS: In a longitudinal design with three measurement points in time (1 week and 1 month apart), 912 women and 214 men were surveyed. Planning, intention, dietary autonomy beliefs, and sex were used to predict fruit and vegetable intake within a conditional process model designed to identify mechanisms of change. RESULTS: The intention-planning-behaviour chain was qualified by a triple interaction involving autonomy beliefs and sex as moderators between intention and planning. Higher dietary autonomy resulted in higher levels of planning fruit and vegetable intake. For men, even in case of higher intention, at least medium levels of autonomy beliefs were necessary to facilitate planning processes. For women, already lower levels of autonomy beliefs can engender postintentional planning strategies and seem to even compensate lower intention. CONCLUSIONS: Intention and planning are key predictors of dietary change. However, these variables work better under specific conditions (with a sufficient level of autonomy), and differently in subgroups (men vs. women). These results may explain the inconsistent findings of previous studies on the mediating effect of planning and allow for a better description of the mechanisms by which intentions may influence behaviour. Statement of contribution What is already known on this subject? The adoption of health-enhancing dietary behaviours can be facilitated by intentions and planning. Planning to eat more fruit and vegetable helps to translate intentions into actual consumption. Fruit and vegetable intake levels are higher in women than in

men. What does this study add? Dietary intentions engender more likely planning processes when perceived autonomy concerning food consumption is high. Dietary autonomy beliefs and sex moderate the intention-planning-behaviour chain. Among men, dietary planning is highest when both intentions and autonomy are high.

Lee, E. J., Allensworth, J. J., Clowers, J. S., & Rosenzweig, H. L. (2015). Aberrant interleukin-1 signalling does not increase susceptibility of mice to NOD2-dependent uveitis. *Clinical and Experimental Ophthalmology, 43*(4), 349-357.

Background: NOD2 is the genetic cause of Blau syndrome, an autoinflammatory disease that manifests as coincident uveitis and arthritis. Since dysregulation of IL-1 signalling is considered a pathogenic mechanism in a number of related autoinflammatory conditions, we examined the extent to which unimpeded interleukin (IL)-1 signalling influences NOD2-dependent inflammation of the eye versus the joint. Methods: Mice deficient for IL-1R antagonist (IL-1Ra) were administered the NOD2 agonist muramyl dipeptide (MDP) by systemic (intraperitoneal) or local (intraocular and/or intra-articular) injections. NOD2-deficient mice received an intraocular injection of recombinant IL-1β. Uveitis was evaluated by intravital videomicroscopy and histopathology, and arthritis was assessed by near-infrared imaging and histopathology. Ocular levels of IL-1α, IL-1β and IL-1Ra were quantified by enzyme-linked immunosorbent assay. Results: IL-1Ra deficiency did not render mice more responsive to systemic exposure of MDP. Despite the increased production of IL-1R agonists IL-1α and IL-1β in response to intraocular injection of MDP, deficiency in IL-1Ra did not predispose mice to MDP-triggered uveitis, albeit intravascular cell rolling and adherence were exacerbated. NOD2 expression was dispensable for the potential of IL-1 to elicit uveitis. However, we find that IL-1Ra does play an important protective role in arthritis induced locally by MDP injection in the joint. Conclusions: Our findings highlight the complexity of NOD2 activation and IL-1 signalling effects that can be compounded by local environmental factors of the target organ. These observations may impact how we understand the molecular mechanisms by which NOD2 influences inflammation of the eye versus joint, and consequently, treatment options for uveitis versus arthritis. © 2014 Royal Australian and New Zealand College of Ophthalmologists.

Levitt, E. S., Abdala, A. P., Paton, J. F., Bissonnette, J. M., & Williams, J. T. (2015). Mu opioid receptor activation hyperpolarizes respiratory-controlling kolliker-fuse neurons and suppresses post-inspiratory drive. *The Journal of Physiology,*

Opioid-induced respiratory effects include aspiration and difficulty swallowing, suggesting impairment of the upper airways. The pontine Kolliker-Fuse (KF) controls upper airway patency and regulates respiration, in particular the inspiratory/expiratory phase transition. Given the importance of the KF in coordinating respiratory pattern, the mechanisms of mu opioid receptor activation in this nucleus were investigated at the systems and cellular level. In anesthetized, vagi-intact rats, injection of opioid agonist DAMGO or [Met5]enkephalin (ME) into the KF reduced respiratory frequency and amplitude. The mu opioid agonist DAMGO applied directly into the KF of the in situ arterially perfused working heart-brainstem preparation of rat resulted in robust apneusis (lengthened low amplitude inspiration due to loss of post-inspiratory drive) that was rapidly reversed by the opioid antagonist naloxone. In brain slice preparations, activation of mu opioid receptors on KF neurons hyperpolarized a distinct population (61%) of neurons. As expected, the opioid-induced hyperpolarization reduced the excitability of the neuron in response to either current injection or local application of glutamate. In voltage-clamp recordings the outward current produced by the opioid agonist ME was concentration-dependent, reversed at the potassium equilibrium potential and was blocked by BaCl2 , characteristics of a G protein-coupled inwardly rectifying potassium (GIRK) conductance. The clinically used drug morphine produced an outward current in KF neurons with similar potency to morphine-mediated currents in locus coeruleus brain slice preparations. Thus, the population of KF neurons that are hyperpolarized by mu opioid agonists are likely mediators of the opioid-induced loss of post-inspiration and induction of apneusis. This article is protected by copyright. All rights reserved.

Liang, C. W., Su, K., Liu, J. J., Dogan, A., & Hinson, H. E. (2015). Timing of deep vein thrombosis formation after aneurysmal subarachnoid hemorrhage. *Journal of Neurosurgery,* , 1-6.

OBJECT Deep vein thrombosis (DVT) is a common complication of aneurysmal subarachnoid hemorrhage (aSAH). The time period of greatest risk for developing DVT after aSAH is not currently known. aSAH induces a prothrombotic state, which may contribute to DVT formation. Using repeated ultrasound screening, the hypothesis that patients would be at greatest risk for

developing DVT in the subacute post-rupture period was tested. METHODS One hundred ninety-eight patients with aSAH admitted to the Oregon Health & Science University Neurosciences Intensive Care Unit between April 2008 and March 2012 were included in a retrospective analysis. Ultrasound screening was performed every 5.2 +/- 3.3 days between admission and discharge. The chi-square test was used to compare DVT incidence during different time periods of interest. Patient baseline characteristics as well as stroke severity and hospital complications were evaluated in univariate and multivariate analyses. RESULTS Forty-two (21%) of 198 patients were diagnosed with DVT, and 3 (2%) of 198 patients were symptomatic. Twenty-nine (69%) of the 42 cases of DVT were first detected between Days 3 and 14, compared with 3 cases (7%) detected between Days 0 and 3 and 10 cases (24%) detected after Day 14 ($p < 0.05$). The postrupture 5-day window of highest risk for DVT development was between Days 5 and 9 (40%, $p < 0.05$). In the multivariate analysis, length of hospital stay and use of mechanical prophylaxis alone were significantly associated with DVT formation. CONCLUSIONS DVT formation most commonly occurs in the first 2 weeks following aSAH, with detection in this cohort peaking between Days 5 and 9. Chemoprophylaxis is associated with a significantly lower incidence of DVT.

Lieberman, D., Brill, J., Canto, M., DeMarco, D., Fennerty, B., Gupta, N., et al. (2015). Management of diminutive colon polyps based on endoluminal imaging. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association,* Diminutive colon polyps, defined as less than or equal to 5mm, are increasingly encountered at colonoscopy. The risk of serious pathology in such polyps is low. There is a risk and cost of resecting all such polyps and sending tissue for pathologic evaluation. Enhancement of endoluminal imaging may enable discrimination of neoplastic versus non-neoplastic polyps. If this discrimination can be performed accurately with high confidence, it may be possible to either resect and discard diminutive adenomas, or inspect and do-not-resect diminutive hyperplastic polyps. In 2011, an expert group recommended thresholds of 90% negative predictive value for adenoma, and 90% accuracy in predicting appropriate surveillance interval. Since 2011, criteria for polyp discrimination have been published and validated by experts and non-expects. In-vivo studies have been performed to compare endoscopic impression and pathologic diagnosis. An

expert panel was convened in late 2014 to review the literature to determine if proposed

thresholds for discrimination can be attained and recommend the next steps for introducing

changes in clinical practice. The review concludes that threshold levels can be achieved with

several endoscopic image enhancements. Next steps to implementation of practice change

include acquiring data on training and competence, determining best practices for auditing

performance, understanding patient education needs, and the potential cost-benefit of such

changes.

Lim, J. Y., & Jeong, J. H. (2015). Cause-specific quantile residual life regression. *Statistical Methods in Medical Research,*

We propose a cause-specific quantile residual life regression where the cause-specific quantile

residual life, defined as the inverse of the cumulative incidence function of the residual life

distribution of a specific type of events of interest conditional on a fixed time point, is log-linear in

observable covariates. The proposed test statistic for the effects of prognostic factors does not

involve estimation of the improper probability density function of the cause-specific residual life

distribution under competing risks. The asymptotic distribution of the test statistic is derived.

Simulation studies are performed to assess the finite sample properties of the proposed

estimating equation and the test statistic. The proposed method is illustrated with a real dataset

from a clinical trial on breast cancer.

Lindemulder, S. J., Stork, L. C., Lu, X., Hunger, S., Neglia, J. P., & Kadan-Lottick, N. S. (2015). Reply to: Obesity is an important health problem in survivors of pediatric acute lymphoblastic leukemia. *Pediatric Blood & Cancer,*

Linfante, I., Walker, G. R., Castonguay, A. C., Dabus, G., Starosciak, A. K., Yoo, A. J., et al. (2015). Predictors of mortality in acute ischemic stroke intervention: Analysis of the north american solitaire acute stroke registry. *Stroke; a Journal of Cerebral Circulation, 46*(8), 2305-2308.
BACKGROUND AND PURPOSE: Failure to recanalize predicts mortality in acute ischemic stroke. In

the North American Solitaire Acute Stroke registry, we investigated parameters associated with

mortality in successfully recanalized patients. METHODS: Logistic regression was used to evaluate

baseline characteristics and recanalization parameters for association with 90-day mortality. A

multivariable model was developed based on backward selection with retention criteria of P/=18, use of rescue therapy (P/=18, use of rescue therapy (P/=18, and use of rescue therapy remained significant independent predictors of 90-day mortality. CONCLUSIONS: Failure to recanalize and presence of symptomatic intracranial hemorrhage resulted in increased mortality. Despite successful recanalization, proximal occlusion, high National Institutes of Health Stroke Scale, and need for rescue therapy were predictors of mortality.

Lipschitz, J. M., Paiva, A. L., Redding, C. A., Butterworth, S., & Prochaska, J. O. (2013). Co-occurrence and coaction of stress management with other health risk behaviors. *Journal of Health Psychology, 20*(7), 1002-1012.

This study provides a preliminary investigation of the role of stress management in multiple behavior change. Risk status on stress management and five health behaviors (healthy eating, exercise, alcohol, smoking, and depression management) was assessed before and after a multiple behavior change intervention. Findings suggested a link between stress management and a worse health risk behavior profile at baseline. Results also showed relationships between improved stress management over 6 months and heightened odds of improving on specific behaviors as well as improving one's overall behavioral risk profile. Particularly strong links between stress management and energy balance and other affective behaviors were observed. © The Author(s) 2013.

Liu, L., Jia, Y., Takusagawa, H. L., Pechauer, A. D., Edmunds, B., Lombardi, L., et al. (2015). Optical coherence tomography angiography of the peripapillary retina in glaucoma. *JAMA Ophthalmology,*
Importance: Vascular factors may have important roles in the pathophysiology of glaucoma. A practical method for the clinical evaluation of ocular perfusion is needed to improve glaucoma management. Objective: To detect peripapillary retinal perfusion in glaucomatous eyes compared with normal eyes using optical coherence tomography (OCT) angiography. Design, Setting, and Participants: Prospective observational study performed from July 24, 2013, to April 17, 2014. Participants were recruited and tested at Casey Eye Institute, Oregon Health & Science University. In total, 12 glaucomatous eyes and 12 age-matched normal eyes were analyzed. The optic disc region was imaged twice using a 3 x 3-mm scan by a 70-kHz, 840-nm-wavelength

spectral OCT system. The split-spectrum amplitude-decorrelation angiography algorithm was used. Peripapillary flow index was calculated as the mean decorrelation value in the peripapillary region, defined as a 700-microm-wide elliptical annulus around the disc. Peripapillary vessel density was the percentage area occupied by vessels. The data statistical analysis was performed from October 30, 2013, to May 30, 2014. Main Outcomes and Measures: Variability was assessed by the coefficient of variation. The Mann-Whitney test was used to compare the 2 groups of eyes. Correlations between vascular and visual field variables were assessed by linear regression analysis. Results: In 12 normal eyes, a dense microvascular network around the disc was visible on OCT angiography. In 12 glaucomatous eyes, this network was visibly attenuated globally and focally. In normal eyes, between-visit reproducibilities of peripapillary flow index and peripapillary vessel density were 4.3% and 2.7% of the coefficient of variation, respectively, while the population variabilities of peripapillary flow index and peripapillary vessel density were 8.2% and 3.0% of the coefficient of variation, respectively. Peripapillary flow index and peripapillary vessel density in glaucomatous eyes were lower than those in normal eyes (P < .001 for both). Peripapillary flow index (Pearson r = -0.808) and peripapillary vessel density (Pearson r = -0.835) were highly correlated with visual field pattern standard deviation in glaucomatous eyes (P = .001 for both). The areas under the receiver operating characteristic curve for normal vs glaucomatous eyes were 0.892 for peripapillary flow index and 0.938 for peripapillary vessel density. Conclusions and Relevance: Using OCT angiography, reduced peripapillary retinal perfusion in glaucomatous eyes can be visualized as focal defects and quantified as peripapillary flow index and peripapillary vessel density, with high repeatability and reproducibility. Quantitative OCT angiography may have value in future studies to determine its potential usefulness in glaucoma evaluation.

Liu, Y., Yasukawa, M., Chen, K., Hu, L., Broaddus, R. R., Ding, L., et al. (2015). Association of somatic mutations of ADAMTS genes with chemotherapy sensitivity and survival in high-grade serous ovarian carcinoma. *JAMA Oncology, 1*(4), 486-494.
IMPORTANCE: Chemotherapy response in the majority of patients with ovarian cancer remains unpredictable. OBJECTIVE: To identify novel molecular markers for predicting chemotherapy response in patients with ovarian cancer. DESIGN, SETTING, AND PARTICIPANTS: Observational

study of genomics and clinical data of high-grade serous ovarian cancer cases with genomic and clinical data made public between 2009 and 2014 via the Cancer Genome Atlas project. MAIN OUTCOMES AND MEASURES: Chemotherapy response (primary outcome) and overall survival (OS), progression-free survival (PFS), and platinum-free duration (secondary outcome). RESULTS: In 512 patients with ovarian cancer with available whole-exome sequencing data, mutations from 8 members of the ADAMTS family (ADAMTS mutations) with an overall mutation rate of approximately 10.4% were associated with a significantly higher chemotherapy sensitivity (100% for ADAMTS-mutated vs 64% for ADAMTS wild-type cases; P < .001) and longer platinum-free duration (median platinum-free duration, 21.7 months for ADAMTS-mutated vs 10.1 months for ADAMTS wild-type cases; P = .001). Moreover, ADAMTS mutations were associated with significantly better OS (hazard ratio [HR], 0.54 [95% CI, 0.42-0.89]; P = .01 and median OS, 58.0 months for ADAMTS-mutated vs 41.3 months for ADAMTS wild-type cases) and PFS (HR, 0.42 [95% CI, 0.38-0.70]; P < .001 and median PFS, 31.8 for ADAMTS-mutated vs 15.3 months for ADAMTS wild-type cases). After adjustment by BRCA1 or BRCA2 mutation, surgical stage, residual tumor, and patient age, ADAMTS mutations were significantly associated with better OS (HR, 0.53 [95% CI, 0.32-0.87]; P = .01), PFS (HR, 0.40 [95% CI, 0.25-0.62]; P < .001), and platinum-free survival (HR, 0.45 [95% CI, 0.28-0.73]; P = .001). ADAMTS-mutated cases exhibited a distinct mutation spectrum and were significantly associated with tumors with a higher genome-wide mutation rate than ADAMTS wild-type cases across the whole exome (median mutation number per sample, 121 for ADAMTS-mutated vs 69 for ADAMTS wild-type cases; P < .001). CONCLUSIONS AND RELEVANCE: ADAMTS mutations may contribute to outcomes in ovarian cancer cases without BRCA1 or BRCA2 mutations and may have important clinical implications.

Lo, S. S. -., Ryu, S., Chang, E. L., Galanopoulos, N., Jones, J., Kim, E. Y., et al. (2015). ACR appropriateness criteria® metastatic epidural spinal cord compression and recurrent spinal metastasis. *Journal of Palliative Medicine, 18*(7), 573-584.
Metastatic epidural spinal cord compression (MESCC) is an oncologic emergency and if left untreated, permanent paralysis will ensue. The treatment of MESCC is governed by disease, patient, and treatment factors. Patient's preferences and goals of care are to be weighed into the

treatment plan. Ideally, a patient with MESCC is evaluated by an interdisciplinary team promptly to determine the urgency of the clinical scenario. Treatment recommendations must take into consideration the risk-benefit profiles of surgical intervention and radiotherapy for the particular individual's circumstance, including neurologic status, performance status, extent of epidural disease, stability of the spine, extra-spinal disease status, and life expectancy. In patients with high spinal instability neoplastic score (SINS) or retropulsion of bone fragments in the spinal canal, surgical intervention should be strongly considered. The rate of development of motor deficits from spinal cord compression may be a prognostic factor for ultimate functional outcome, and should be taken into account when a treatment recommendation is made. The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every three years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment. © Copyright 2015, Mary Ann Liebert, Inc.

Long, T. H., Lawce, H., Durum, C., Moore, S. R., Olson, S. B., Gatter, K., et al. (2015). The new equivocal: Changes to HER2 FISH results when applying the 2013 ASCO/CAP guidelines. *American Journal of Clinical Pathology, 144*(2), 253-262.
OBJECTIVES: Human epidermal growth factor receptor 2 (HER2, ERBB2) testing is an important prognostic/predictive marker in breast cancer management, especially in selecting HER2-targeted treatment. American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines address HER2 status and were recently revised in 2013, replacing the 2007 version. For in situ hybridization interpretation, 2013 guidelines return to the prior threshold of a HER2/CEP17 ratio of 2.0 or greater for positive and eliminate 1.8 to 2.2 as the equivocal range. Also, the HER2 signal/nucleus ratio is accounted for, with 6.0 or greater for positive and 4.0 to less than 6.0 for equivocal, even in cases with a HER2/CEP17 ratio less than 2.0. METHODS: With institutional review board approval, we reviewed our 2006 to 2012 HER2 fluorescence in situ hybridization (FISH) results and classified them according to both the 2007 and 2013 guidelines

as negative, positive, or equivocal. RESULTS: Of 717 HER2 FISH results, 55 (7.7%) changed category when reassessed by 2013 guidelines. Nineteen of 25 results in the 2007 equivocal category were reassigned as positive (n = 13) or negative (n = 6). Thirty-five previously negative cases became equivocal in the 2013 scheme, 12 of these with 1+ immunohistochemistry. The positive category increased from 71 to 85. CONCLUSIONS: The 2013 ASCO/CAP guidelines increased the number of HER2 FISH positive and equivocal results. The equivocal group is substantially different, posing a dilemma for clinical management.

Lorenz, J. M., Al-Refaie, W. B., Cash, B. D., Gaba, R. C., Gervais, D. A., Gipson, M. G., et al. (2015). ACR appropriateness criteria radiologic management of infected fluid collections. *Journal of the American College of Radiology : JACR,*
The best management of infected fluid collections depends on a careful assessment of clinical and anatomic factors as well as an up-to-date review of the published literature, to be able to select from a host of multidisciplinary treatment options. This article reviews conservative, radiologic, endoscopic, and surgical options and their best application to infected fluid collections as determined by the ACR Appropriateness Criteria Expert Panel on Interventional Radiology. The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every three years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals, and the application, by the panel, of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Love, J. N., Yarris, L. M., Ankel, F. K., & Council of Emergency Medicine Residency Directors (CORD). (2015). Emergency medicine milestones: The next step. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine, 22*(7), 847-848.

Loyo, M., & Wang, T. D. (2015). Management of the deviated nasal dorsum. *Facial Plastic Surgery : FPS, 31*(3), 216-227.
The deviated nasal dorsum veers off the ideal straight vertical orientation at midline. Deviations

in the dorsum lead to functional and aesthetic consequences that frequently prompt the patient to seek consultation with a rhinoplasty surgeon. Inability to breathe through the nose and self-image perception significantly detracts from the patient's quality of life. Correction of the deviated nasal dorsum represents a challenge for the rhinoplasty surgeon. Anatomic correction of deviations is the goal. Straightening a deviated nasal dorsum will require maneuvers to realign the nose distinct from traditional aesthetic rhinoplasty techniques. The nasal dorsum is formed by the three-dimensional structures of the septum, the bony nasal pyramid, and the cartilaginous nasal midvault. Restoring the position of the septum at midline is the first step in providing adequate support to the nasal architecture. Extracorporeal septoplasty and anterior septal transplant are often necessary techniques to correct the septum and achieve dorsal correction. Subsequently, asymmetric maneuvers to bony dorsum and midvault are performed to restore symmetry. Asymmetric hump reduction and nasal osteotomies are often necessary. Supporting the midvault to avoid nasal collapse often requires asymmetric maneuvers to the upper lateral cartilages and asymmetric spreader grafts. Finally, camouflaging grafts to the nasal dorsum may be necessary. Significant rigidity and memory of the native tissues must be overcome to successfully straighten a nose. The surgeon who can master the deviated dorsum will significantly improve the appearance and quality of life of the patients he or she treats.

Luk, L. J., Steele, T. O., Mace, J. C., Soler, Z. M., Rudmik, L., & Smith, T. L. (2015). Health utility outcomes in patients undergoing medical management for chronic rhinosinusitis: A prospective multiinstitutional study. *International Forum of Allergy & Rhinology,*
BACKGROUND: A health utility value represents an individual's preference for living in a specific health state and is used in cost-utility analyses. This study investigates the impact of continuing medical therapy on health utility outcomes in patients with chronic rhinosinusitis (CRS). METHODS: The Medical Outcomes Study Short Form-6D (SF-6D) questionnaire was administered to patients prospectively enrolled in a longitudinal study examining treatment outcomes for CRS. Patients were prescribed robust, initial medical therapy and then elected to continue with medical therapy (n = 40) or undergo endoscopic sinus surgery (ESS), followed by medical therapy (n = 152). Patients observed through treatment crossover to ESS were also evaluated (n = 20). Health utility values (SF-6D) were generated at baseline, 6-months, and 12-months follow-up for

both cohorts and evaluated using repeated measures analysis of variance (ANOVA). RESULTS: Treatment crossover patients were found to have a significantly higher prevalence of previous sinus surgery compared to medical management (chi2 = 6.91; p = 0.009) and surgical intervention (chi2 = 8.11; p = 0.004) subgroups. Mean baseline utility value for the medical therapy cohort was significantly better compared to the ESS cohort (mean +/- standard deviation; 0.76 +/- 0.12 vs 0.70 +/- 0.15; p = 0.023). Significant improvement in health utility was reported in the ESS cohort (F(2) = 37.69; p < 0.001), whereas values remained stable, without significant improvement, in both the medical therapy cohort (F(2) = 0.03; p = 0.967) and treatment crossover cohort (F(2) = 2.36; p = 0.115). CONCLUSION: Patients electing continued medical management report better baseline health utility compared to patients electing ESS. Patients electing ESS show significant improvement in health utility, whereas those electing continued medical management demonstrate stable health utility over 12 months.

Lyons, B. E., Austin, D., Seelye, A., Petersen, J., Yeargers, J., Riley, T., et al. (2015). Pervasive computing technologies to continuously assess alzheimer's disease progression and intervention efficacy. *Frontiers in Aging Neuroscience, 7*, 102.

Traditionally, assessment of functional and cognitive status of individuals with dementia occurs in brief clinic visits during which time clinicians extract a snapshot of recent changes in individuals' health. Conventionally, this is done using various clinical assessment tools applied at the point of care and relies on patients' and caregivers' ability to accurately recall daily activity and trends in personal health. These practices suffer from the infrequency and generally short durations of visits. Since 2004, researchers at the Oregon Center for Aging and Technology (ORCATECH) at the Oregon Health and Science University have been working on developing technologies to transform this model. ORCATECH researchers have developed a system of continuous in-home monitoring using pervasive computing technologies that make it possible to more accurately track activities and behaviors and measure relevant intra-individual changes. We have installed a system of strategically placed sensors in over 480 homes and have been collecting data for up to 8 years. Using this continuous in-home monitoring system, ORCATECH researchers have collected data on multiple behaviors such as gait and mobility, sleep and activity patterns, medication adherence, and computer use. Patterns of intra-individual variation detected in each of these

areas are used to predict outcomes such as low mood, loneliness, and cognitive function. These methods have the potential to improve the quality of patient health data and in turn patient care especially related to cognitive decline. Furthermore, the continuous real-world nature of the data may improve the efficiency and ecological validity of clinical intervention studies.

Ma, H., Folmes, C. D., Wu, J., Morey, R., Mora-Castilla, S., Ocampo, A., et al. (2015). Metabolic rescue in pluripotent cells from patients with mtDNA disease. *Nature,*

Mitochondria have a major role in energy production via oxidative phosphorylation, which is dependent on the expression of critical genes encoded by mitochondrial (mt)DNA. Mutations in mtDNA can cause fatal or severely debilitating disorders with limited treatment options. Clinical manifestations vary based on mutation type and heteroplasmy (that is, the relative levels of mutant and wild-type mtDNA within each cell). Here we generated genetically corrected pluripotent stem cells (PSCs) from patients with mtDNA disease. Multiple induced pluripotent stem (iPS) cell lines were derived from patients with common heteroplasmic mutations including 3243A>G, causing mitochondrial encephalomyopathy and stroke-like episodes (MELAS), and 8993T>G and 13513G>A, implicated in Leigh syndrome. Isogenic MELAS and Leigh syndrome iPS cell lines were generated containing exclusively wild-type or mutant mtDNA through spontaneous segregation of heteroplasmic mtDNA in proliferating fibroblasts. Furthermore, somatic cell nuclear transfer (SCNT) enabled replacement of mutant mtDNA from homoplasmic 8993T>G fibroblasts to generate corrected Leigh-NT1 PSCs. Although Leigh-NT1 PSCs contained donor oocyte wild-type mtDNA (human haplotype D4a) that differed from Leigh syndrome patient haplotype (F1a) at a total of 47 nucleotide sites, Leigh-NT1 cells displayed transcriptomic profiles similar to those in embryo-derived PSCs carrying wild-type mtDNA, indicative of normal nuclear-to-mitochondrial interactions. Moreover, genetically rescued patient PSCs displayed normal metabolic function compared to impaired oxygen consumption and ATP production observed in mutant cells. We conclude that both reprogramming approaches offer complementary strategies for derivation of PSCs containing exclusively wild-type mtDNA, through spontaneous segregation of heteroplasmic mtDNA in individual iPS cell lines or mitochondrial replacement by SCNT in homoplasmic mtDNA-based disease.

Mann, R., Sadosky, A., Schaefer, C., Baik, R., Parsons, B., Nieshoff, E., et al. (2015). Burden of HIV-
 related neuropathic pain in the united states. *Journal of the International Association of Providers
 of AIDS Care,*
 BACKGROUND: HIV-related neuropathic pain (HIV-NeP) is common; however, the burden of HIV-
 NeP is not well-understood. METHODS: The cross-sectional study aimed to characterize the HIV-
 NeP burden. A total of 103 patients with HIV-NeP recruited during routine office visits completed
 a questionnaire to assess patient-reported outcomes, including pain severity, health status,
 sleep, mood, and lost productivity. Physicians completed a 6-month retrospective chart review.
 RESULTS: The sample was predominantly male and not employed for pay. A majority (75.7%) of
 patients experienced moderate or severe pain. Pain interference, general health, physical health,
 and depression were worse among patients with more severe pain (all Ps < .006). Most (87.4%)
 patients were prescribed at least 1 medication for NeP. HIV-related neuropathic pain was
 associated with 36.1% work impairment. Adjusted annualized costs increased with increasing
 pain severity (P < .0001). CONCLUSION: The impact of HIV-NeP on health status, physical
 function, and depression increases with severity, resulting in substantial clinical and economic
 burden.

Marcus, G. M., & Dewland, T. A. (2015). Premature atrial contractions: A wolf in sheep's clothing?
 Journal of the American College of Cardiology, 66(3), 242-244.

Markway, B. D., Cho, H., Zilberman-Rudenko, J., Holden, P., McAlinden, A., & Johnstone, B. (2015).
 Hypoxia-inducible factor 3-alpha expression is associated with the stable chondrocyte phenotype.
 Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society,
 The hypoxia-inducible factors HIF-1alpha and HIF-2alpha are important regulators of the
 chondrocyte phenotype but little is known about HIF-3alpha in cartilage. The objective of this
 study was to characterize HIF-3alpha (HIF3A) expression during chondrocyte differentiation in
 vitro and in native cartilage tissues. HIF3A, COL10A1, and MMP13 were quantified in
 mesenchymal stem cells (MSCs) and articular chondrocytes from healthy and osteoarthritic (OA)
 tissue in three-dimensional cultures and in human embryonic epiphyses and adult articular
 cartilage. HIF3A was found to have an inverse association with hypertrophic markers COL10A1

and MMP13 in chondrogenic cells and tissues. In healthy chondrocytes, HIF3A was induced by dexamethasone and increased during redifferentiation. By comparison, HIF3A expression was extremely low in chondrogenically differentiated MSCs expressing high levels of COL10A1 and MMP13. HIF3A was also lower in redifferentiated OA chondrocytes than in healthy chondrocytes. In human embryonic epiphyseal tissue, HIF3A expression was lowest in the hypertrophic zone. Distinct splice patterns were also found in embryonic cartilage when compared with adult articular cartilage and redifferentiated chondrocytes. These in vitro and in vivo findings suggest that HIF3A levels are indicative of the hypertrophic state of chondrogenic cells and one or more splice variants may be important regulators of the chondrocyte phenotype. (c) 2015 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res.

McCarthy, M. S., & Martindale, R. G. (2015). What's on the menu? delivering evidence-based nutritional therapy. *Nursing, 45*(8), 36-43.

McClintic, S. M., Jia, Y., Huang, D., & Bailey, S. T. (2015). Optical coherence tomographic angiography of choroidal neovascularization associated with central serous chorioretinopathy. *JAMA Ophthalmology,*

McClintic, S. M., Kim, D. Y., Fingler, J., Garcia, S., Zawadzki, R. J., Morse, L. S., et al. (2015). Detection of pigment epithelial detachment vascularization in age-related macular degeneration using phase-variance OCT angiography. *Clinical Ophthalmology (Auckland, N.Z.), 9*, 1299-1305. PURPOSE: To demonstrate the use of phase-variance optical coherence tomography (PV-OCT) angiography for detection of pigment epithelial detachment (PED) vascularization in age-related macular degeneration (AMD). PATIENTS AND METHODS: Patients with PEDs and exudative AMD were evaluated by the Retina Services at the University of California, Davis, and the University of California, San Francisco. Each subject underwent fluorescein angiography and structural optical coherence tomography (OCT). Phase-variance OCT analysis was used to create angiographic images of the retinal and choroidal vasculature. PV-OCT-generated B-scans were superimposed on structural OCT B-scans to allow easy identification of perfused vascular structures. RESULTS: Three patients with vascularized PEDs were imaged with PV-OCT, and each was found to have a vascular signal extending from the choroid into the hyperreflective substance of the PED. Two

patients who had no evidence of PED vascularization on fluorescein angiography did not have vascular signals within their PEDs on PV-OCT. CONCLUSION: Structural OCT and PV-OCT images can be combined to create composite B-scans that offer high-resolution views of the retinal tissue along with dynamic vascular visualization. This technique offers a fast, noninvasive method for detecting vascularization of PEDs in AMD and may aid in the early detection of neovascular disease.

McLarry, J., Broberg, C., Opotowsky, A. R., Kaufman, T., Stout, K., & Burchill, L. J. (2014). Defining heart failure in adult congenital heart disease. *Progress in Pediatric Cardiology, 38*(1-2), 3-7. As the adult congenital heart disease (ACHD) population expands and ages, the incidence and prevalence of heart failure will rise. This poses several challenges, all complicated by our nascent understanding of heart failure epidemiology, pathophysiology and management in adults with congenital heart disease. Current definitions extrapolated from acquired heart failure often disregard the unique pathophysiology of heart failure in adults with congenital heart disease. Others have suggested that congenital heart disease is the 'original heart failure syndrome' implying that all ACHD patients are destined to manifest heart failure. Neither the adoption of acquired heart failure definitions nor the belief that heart failure is the common ultimate manifestation of ACHD has advanced the care of ACHD patients. The absence of a comprehensive definition that focuses on common themes while recognizing the unique manifestations of heart failure in ACHD stifles research progress and has translated to a paucity of ACHD specific recommendations in existing heart failure guidelines. Since many ACHD heart failure patients do not meet standard definitions of heart failure their access to potentially beneficial interventions such as cardiac rehabilitation is restricted by payers and regulators taking a narrow view of acquired heart failure guidelines. ACHD heart failure definitions that can be applied in the clinical and research setting are needed to guide treatment, facilitate communication between specialists, determine the prevalence and incidence of heart failure in AHCD, and improve ACHD patients' access to heart failure treatments. The purpose of this review is to understand how heart failure has been considered and defined in the existing ACHD literature and to highlight the need for a definition of heart failure applicable to ACHD. © 2014 Elsevier Ireland Ltd.

Mench, A., Lipnharski, I., Carranza, C., Sinclair, L., Lamoureux, R., Smajdor, L., et al. (2015). SU-F-207-02: Use of postmortem subjects for subjective image quality assessment in abdominal CT protocols with iterative reconstruction. *Medical Physics, 42*(6), 3542.

PURPOSE: New radiation dose reduction technologies are emerging constantly in the medical imaging field. The latest of these technologies, iterative reconstruction (IR) in CT, presents the ability to reduce dose significantly and hence provides great opportunity for CT protocol optimization. However, without effective analysis of image quality, the reduction in radiation exposure becomes irrelevant. This work explores the use of postmortem subjects as an image quality assessment medium for protocol optimizations in abdominal CT. METHODS: Three female postmortem subjects were scanned using the Abdomen-Pelvis (AP) protocol at reduced minimum tube current and target noise index (SD) settings of 12.5, 17.5, 20.0, and 25.0. Images were reconstructed using two strengths of iterative reconstruction. Radiologists and radiology residents from several subspecialties were asked to evaluate 8 AP image sets including the current facility default scan protocol and 7 scans with the parameters varied as listed above. Images were viewed in the soft tissue window and scored on a 3-point scale as acceptable, borderline acceptable, and unacceptable for diagnosis. The facility default AP scan was identified to the reviewer while the 7 remaining AP scans were randomized and de-identified of acquisition and reconstruction details. The observers were also asked to comment on the subjective image quality criteria they used for scoring images. This included visibility of specific anatomical structures and tissue textures. RESULTS: Radiologists scored images as acceptable or borderline acceptable for target noise index settings of up to 20. Due to the postmortem subjects' close representation of living human anatomy, readers were able to evaluate images as they would those of actual patients. CONCLUSION: Postmortem subjects have already been proven useful for direct CT organ dose measurements. This work illustrates the validity of their use for the crucial evaluation of image quality during CT protocol optimization, especially when investigating the effects of new technologies.

Meyersohn, N. M., Ghemigian, K., Shapiro, M. D., Shah, S. V., Ghoshhajra, B. B., & Ferencik, M. (2015). Role of computed tomography in assessment of the thoracic aorta. *Current Treatment Options in Cardiovascular Medicine, 17*(8)

Thoracic aortic disease is increasing in prevalence and can result in serious morbidity and mortality. Computed tomography (CT) angiography is an important imaging modality for assessment of thoracic aortic pathology due to wide availability, rapid acquisition, reproducibility, superior spatial and temporal resolution, and capability for 3D image post-processing. CT is the preferred imaging modality in the acute setting to rapidly identify patients with acute aortic syndromes including dissection, intramural hematoma, and penetrating aortic ulcer. CT also plays an important role in post-procedural surveillance of the thoracic aorta for early and late complications from open or endovascular repair. Incidentally detected thoracic aortic aneurysms and congenital aortic anomalies such as coarctation can be thoroughly characterized and followed over time for potential elective intervention. Drawbacks of CT include exposure to radiation and iodinated contrast media; however, recent strategies for dose reduction and contrast optimization have significantly decreased these risks. Electrocardiogram (ECG)-gated CT angiography provides additional information about the aortic root, coronary arteries, and other cardiac structures without motion artifacts. © 2015, Springer Science+Business Media New York.

Miglioretti, D. L., Ichikawa, L., Smith, R. A., Bassett, L. W., Feig, S. A., Monsees, B., et al. (2015). Criteria for identifying radiologists with acceptable screening mammography interpretive performance on basis of multiple performance measures. *American Journal of Roentgenology, 204*(4), W486-W491.

Objective. Using a combination of performance measures, we updated previously proposed criteria for identifying physicians whose performance interpreting screening mammography may indicate suboptimal interpretation skills. Materials and Methods. In this study, six expert breast imagers used a method based on the Angoff approach to update criteria for acceptable mammography performance on the basis of two sets of combined performance measures: set 1, sensitivity and specificity for facilities with complete capture of false-negative cancers; and set 2, cancer detection rate (CDR), recall rate, and positive predictive value of a recall (PPV1) for facilities that cannot capture false-negative cancers but have reliable cancer follow-up information for positive mammography Results. Decisions were informed by normative data from the Breast Cancer Surveillance Consortium (BCSC). Results. Updated combined ranges for acceptable sensitivity and specificity of screening mammography are sensitivity. 80% and

specificity. 85% or sensitivity 75.79% and specificity 88.97%. Updated ranges for CDR, recall rate, and PPV1 are: CDR. 6 per 1000, recall rate 3.20%, and any PPV1; CDR 4.6 per 1000, recall rate 3.15%, and PPV1. 3%; or CDR 2.5.4.0 per 1000, recall rate 5.12%, and PPV1 3.8%. Using the original criteria, 51% of BCSC radiologists had acceptable sensitivity and specificity; 40% had acceptable CDR, recall rate, and PPV1. Using the combined criteria, 69% had acceptable sensitivity and specificity and 62% had acceptable CDR, recall rate, and PPV1. Conclusion. The combined criteria improve previous criteria by considering the interrelationships of multiple performance measures and broaden the acceptable performance ranges compared with previous criteria based on individual measures. © American Roentgen Ray Society.

Miley, G. P., Pou, S., Winter, R., Nilsen, A., Li, Y., Kelly, J. X., et al. (2015). ELQ-300 prodrugs for enhanced delivery and single dose cure of malaria. *Antimicrobial Agents and Chemotherapy,* ELQ-300 is a preclinical candidate that targets the liver and blood stages of falciparum malaria, as well as the forms that are crucial to transmission of disease: gametocytes, zygotes, and ookinetes. A significant obstacle to the clinical development of ELQ-300 relates to its physicochemical properties. Its relatively poor aqueous solubility and high crystallinity limits absorption to the degree that only low blood concentrations can be achieved following oral dosing. While these low blood concentrations are sufficient for therapy, the levels are too low to establish an acceptable safety margin required by regulatory agencies for clinical development. One way to address the challenging physicochemical properties of ELQ-300 is through the development of prodrugs. Here we profile ELQ-337, a bioreversible O-linked carbonate ester prodrug of the parent molecule. At the molar equivalent dose of 3 mg/kg, the delivery of ELQ-300 from ELQ-337 is enhanced by 3- to 4-fold, reaching a Cmax of 5.9 muM by 6 h after oral administration. And unlike ELQ-300 at any dose, ELQ-337 provides single-dose cures of patent malaria infections in mice at low single digit mg/kg doses. Our findings show that the prodrug strategy represents a viable approach to overcome the physicochemical limitations of ELQ-300 to deliver the active drug to the bloodstream at concentrations sufficient for safety and toxicology studies as well as achieving single dose cures.

Mitchell, J. E., King, W. C., Pories, W., Wolfe, B., Flum, D. R., Spaniolas, K., et al. (2015). Binge

   eating disorder and medical comorbidities in bariatric surgery candidates. *International Journal of*

   Eating Disorders, 48(5), 471-476.

   Objective To determine whether binge eating disorder (BED) status is associated with medical

   comorbidities in obese adults scheduled for bariatric surgery. Method The study utilized

   Longitudinal Assessment of Bariatric Surgery-2 data obtained from six clinical centers around the

   United States. This is a well-phenotyped cohort of individuals who were evaluated within 30 days

   before their scheduled surgery using standardized protocols. In the cohort, 350 participants were

   classified as having BED and 1,875 as not having BED (non-BED). Multivariable logistic regression

   was used to determine whether BED status was independently related to medical comorbidities.

   As an exploratory analysis, significance was based on nominal p-values (p<.05). Holm's-adjusted

   p-values were also reported. Results After adjusting for age, sex, education, and body mass

   index, BED status was found to be independently associated with four of the 15 comorbidities

   (i.e., impaired glucose levels (odds ratio [OR]=1.45 (95% confidence interval [CI]: 1.12-1.87)),

   high triglycerides (OR=1.28 (95% CI: 1.002-1.63)), and urinary incontinence (OR=1.30 (95%

   CI: 1.02-1.66)), all being more common among the BED sample, and severe walking limitations

   being less common in the BED sample (OR=0.53 (95% CI: 0.29-0.96)). With further adjustment

   for psychiatric/emotional health indicators, BED status was independently associated with three

   comorbidities (impaired glucose levels (OR=1.36 (95% CI: 1.04-1.79)), cardiovascular disease

   (OR=0.50 (95% CI: 0.30-0.86)), and severe walking limitations (OR=0.38 (95% CI: 0.19-0.77)).

   However, Holm's-adjusted p-values for all variables were greater than.05. Discussion The results

   suggest the possibility of a contribution of BED to risk of specific medical comorbidities in

   severely obese adults. © 2014 Wiley Periodicals, Inc.

Mitin, T., & Kubicky, C. D. (2015). The use of hypofractionated whole breast irradiation in treatment of

   patients with early-stage breast cancer in the united states. *JAMA Oncology, 1*(2), 245-246.

Mitrugno, A., Tormoen, G. W., Kuhn, P., & McCarty, O. J. (2015). The prothrombotic activity of cancer

   cells in the circulation. *Blood Reviews,*

   The hemostatic system is often subverted in patients with cancer, resulting in life-threatening

venous thrombotic events. Despite the multifactorial and complex etiology of cancer-associated thrombosis, changes in the expression and activity of cancer-derived tissue factor (TF) - the principle initiator of the coagulation cascade - are considered key to malignant hypercoagulopathy and to the pathophysiology of thrombosis. However, many of the molecular and cellular mechanisms coupling the hemostatic degeneration to malignancy remain largely uncharacterized. In this review we discuss some of the tumor-intrinsic and tumor-extrinsic mechanisms that may contribute to the prothrombotic state of cancer, and we bring into focus the potential for circulating tumor cells (CTCs) in advancing our understanding of the field. We also summarize the current status of anti-coagulant therapy for the treatment of thrombosis in patients with cancer.

Moreira, D. M., Howard, L. E., Sourbeer, K. N., Amarasekara, H. S., Chow, L. C., Cockrell, D. C., et al. (2015). Predicting bone scan positivity in non-metastatic castration-resistant prostate cancer. *Prostate Cancer and Prostatic Diseases,*

BACKGROUND: To evaluate PSA levels and kinetic cutoffs to predict positive bone scans for men with non-metastatic castration-resistant prostate cancer (CRPC) from the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort. METHODS: Retrospective analysis of 531 bone scans of 312 clinically CRPC patients with no known metastases at baseline treated with a variety of primary treatment types in the SEARCH database. The association of patients' demographics, pathological features, PSA levels and kinetics with risk of a positive scan was tested using generalized estimating equations. RESULTS: A total of 149 (28%) scans were positive. Positive scans were associated with younger age (odds ratio (OR)=0.98; P=0.014), higher Gleason scores (relative to Gleason 2-6, Gleason 3+4: OR=2.03, P=0.035; Gleason 4+3 and 8-10: OR=1.76, P=0.059), higher prescan PSA (OR=2.11; P5, 5-14.9, 15-49.9 and greater than or equal to50 ng ml-1, respectively (P-trend <0.001). Men with PSADT greater than or equal to15, 9-14.9, 3-8.9 and <3 months had a scan positivity of 11, 22, 34 and 47%, correspondingly (P-trend <0.001). Tables were constructed using PSA and PSADT to predict the likelihood of a positive bone scan. CONCLUSIONS: PSA levels and kinetics were associated with positive bone scans. We developed tables to predict the risk of positive bone scans by PSA and PSADT. Combining PSA levels and

kinetics may help select patients with CRPC for bone scans..Prostate Cancer and Prostatic Disease advance online publication, 26 May 2015; doi:10.1038/pcan.2015.25.

Morry, J., Ngamcherdtrakul, W., Gu, S., Goodyear, S. M., Castro, D. J., Reda, M. M., et al. (2015). Dermal delivery of HSP47 siRNA with NOX4-modulating mesoporous silica-based nanoparticles for treating fibrosis. *Biomaterials, 66*, 41-52.

Fibrotic diseases such as scleroderma have been linked to increased oxidative stress and upregulation of pro-fibrotic genes. Recent work suggests a role of NADPH oxidase 4 (NOX4) and heat shock protein 47 (HSP47) in inducing excessive collagen synthesis, leading to fibrotic diseases. Herein, we elucidate the relationship between NOX4 and HSP47 in fibrogenesis and propose to modulate them altogether as a new strategy to treat fibrosis. We developed a nanoparticle platform consisting of polyethylenimine (PEI) and polyethylene glycol (PEG) coating on a 50-nm mesoporous silica nanoparticle (MSNP) core. The nanoparticles effectively delivered small interfering RNA (siRNA) targeting HSP47 (siHSP47) in an in vitro model of fibrosis based on TGF-beta stimulated fibroblasts. The MSNP core also imparted an antioxidant property by scavenging reactive oxygen species (ROS) and subsequently reducing NOX4 levels in the in vitro fibrogenesis model. The nanoparticle was far superior to n-acetyl cysteine (NAC) at modulating pro-fibrotic markers. In vivo evaluation was performed in a bleomycin-induced scleroderma mouse model, which shares many similarities to human scleroderma disease. Intradermal administration of siHSP47-nanoparticles effectively reduced HSP47 protein expression in skin to normal level. In addition, the antioxidant MSNP also played a prominent role in reducing the pro-fibrotic markers, NOX4, alpha smooth muscle actin (alpha-SMA), and collagen type I (COL I), as well as skin thickness of the mice.

Mularski, R. A., & Rocker, G. (2015). Managing dyspnea in advanced chronic obstructive pulmonary disease: Balancing all the evidence. *Annals of the American Thoracic Society, 12*(7), 978-980.

Nagata, T., Suzuki, F., & Teo, A. R. (2015). Generalized social anxiety disorder: A still-neglected anxiety disorder 3 decades since liebowitz's review. *Psychiatry and Clinical Neurosciences,*

In the 3 decades since Liebowitz's review of 'a neglected anxiety disorder,' controversy and challenges have remained in the study of social anxiety disorder (SAD). This review examines

evidence around the classification and subtyping of SAD, focusing on generalized SAD. Substantial discrepancies and variation in definition, epidemiology, assessment, and treatment of generalized SAD exist as the international literature on it has grown. In East Asian cultures in particular, study of taijin kyofusho has been important to a broadened conceptualization of SAD into generalized SAD. Despite important progress with biological and other studies, many challenges in the understanding of generalized SAD will remain in the years to come.

Napier, R. J., Adams, E. J., Gold, M. C., & Lewinsohn, D. M. (2015). The role of mucosal associated invariant T cells in antimicrobial immunity. *Frontiers in Immunology, 6*, 344.

Mucosal associated invariant T (MAIT) cells are an innate-like T cell subset prevalent in humans and distributed throughout the blood and mucosal sites. Human MAIT cells are defined by the expression of the semi-invariant TCRalpha chain TRAV1-2/TRAJ12/20/33 and are restricted by the non-polymorphic major histocompatibility complex (MHC) class I-like molecule, MHC-related protein 1, MR1. MAIT cells are activated by small organic molecules, derived from the riboflavin biosynthesis pathway of bacteria and fungi, presented by MR1. Traditionally, MAIT cells were thought to recognize a limited number of antigens due to usage of an invariant TCRalpha chain and restriction by a non-polymorphic MHC molecule. However, recent studies demonstrate that the TCR repertoire of MAIT cells is more heterogeneous, suggesting there is a more diverse array of MR1 antigens that MAIT cells can recognize. In response to infected cells, MAIT cells produce the pro-inflammatory cytokines, IFN-gamma and TNF, and are cytolytic. Studies performed in MR1-deficient mice suggest that MAIT cells can provide anti-bacterial control within the first few days post-infection, as well as contribute to enhanced adaptive immunity in murine models of respiratory infections. In humans, the role of MAIT cells is unclear; however, evidence points to interplay between MAIT cells and microbial infections, including Mycobacterium tuberculosis. Given that MAIT cells are pro-inflammatory, serve in early control of bacterial infections, and appear enriched at tissue sites where microbes interface and gain access to the body, we postulate that they play an important role in antimicrobial immune responses. In this review, we discuss the most recent studies on the function and phenotype of MAIT cells, including their TCR diversity and antigenic repertoire, with a focus on the contribution of human MAIT cells in the immune response to microbial infection.

Nazi, K. M., Turvey, C. L., Klein, D. M., Hogan, T. P., & Woods, S. S. (2015). VA OpenNotes: Exploring the experiences of early patient adopters with access to clinical notes. *Journal of the American Medical Informatics Association : JAMIA, 22*(2), 380-389.

OBJECTIVE: To explore the experience of early patient adopters who accessed their clinical notes online using the Blue Button feature of the My HealtheVet portal. METHODS: A web-based survey of VA patient portal users from June 22 to September 15, 2013. RESULTS: 33.5% of respondents knew that clinical notes could be viewed, and nearly one in four (23.5%) said that they had viewed their notes at least once. The majority of VA Notes users agreed that accessing their notes will help them to do a better job of taking medications as prescribed (80.1%) and be better prepared for clinic visits (88.6%). Nine out of 10 users agreed that use of visit notes will help them understand their conditions better (91.8%), and better remember the plan for their care (91.9%). In contrast, 87% disagreed that VA Notes will make them worry more, and 88.4% disagreed that access to VA Notes will be more confusing than helpful. Users who had either contacted their provider or healthcare team (11.9%) or planned to (13.5%) primarily wanted to learn more about a health issue, medication, or test results (53.7%). CONCLUSIONS: Initial assessment of the patient experience within the first 9 months of availability provides evidence that patients both value and benefit from online access to clinical notes. These findings are congruent with OpenNotes study findings on a broader scale. Additional outreach and education is needed to enhance patient awareness. Healthcare professionals should author notes keeping in mind the opportunity patient access presents for enhanced communication.

Nelson, H. D., Weerasinghe, R., Wang, L., & Grunkemeier, G. (2015). Mammography screening in a large health system following the U.S. preventive services task force recommendations and the affordable care act. *PloS One, 10*(6), e0131903.

BACKGROUND: Practice recommendations for mammography screening were issued by the U.S. Preventive Services Task Force in 2009 and expansion of insurance coverage was provided under the Patient Protection and Affordable Care Act soon thereafter, yet the influence of these changes on screening practices in the United States is not known. METHODS: To determine changes in mammography screening and their associations with new practice recommendations and the Affordable Care Act, we examined patient-level data from 249,803 screening mammograms from

January 1, 2008 through December 31, 2012 in a large community-based health system in the northwestern United States. Associations were determined by an intervention analysis of time-series data method. RESULTS: Among women screened, 64% were age 50-74 years; 84% self-identified as white race; 62% had commercial insurance; and 70% were seen in facilities located in metropolitan areas. Practice recommendations were associated with decreased screening volumes among women age /=75 (-54.7 mammograms/month; -10.0% change; P/=75 (-54.7 mammograms/month; -10.0% change; P/=75; increases for age 40-49 were of borderline statistical significance (+56.9 mammograms/month; +6% change; P=0.06). Practice recommendations were also associated with decreased screening for women with commercial insurance, while the Affordable Care Act was associated with increased screening for women with Medicare, Medicaid, or other noncommercial sources of payment. CONCLUSIONS: Mammography screening volumes in a large community health system decreased among women age /=75 in association with new U.S. Preventive Services Task Force practice recommendations, while insurance coverage changes under the Affordable Care Act were associated with increased screening volumes among women age 50-74.

Nelson, J. W., Zhang, W., Alkayed, N. J., & Koerner, I. P. (2015). Peroxisomal translocation of soluble epoxide hydrolase protects against ischemic stroke injury. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism,* Soluble epoxide hydrolase (sEH) contributes to cardiovascular disease, including stroke, although the exact mechanism remains unclear. While primarily a cytosolic enzyme, sEH can translocate into peroxisomes. The relevance of this for stroke injury is not understood. We tested the hypothesis that sEH-mediated injury is tied to the cytoplasmic localization. We found that a human sEH variant possessing increased affinity to peroxisomes reduced stroke injury in sEH-null mice, whereas infarcts were significantly larger when peroxisomal translocation of sEH was disrupted. We conclude that sEH contributes to stroke injury only when localized in the cytoplasm, while peroxisomal sEH may be protective.Journal of Cerebral Blood Flow & Metabolism advance online publication, 1 July 2015; doi:10.1038/jcbfm.2015.159.

NeSmith, M., Jou, J., Fennerty, M. B., Kolbeck, K. J., Lee, B., & Ahn, J. (2014). Transjugular

intrahepatic portosystemic shunt prior to endoscopic mucosal resection for barrett's esophagus in

the setting of varices. *ACG Case Reports Journal, 1*(4), 189-192.

Patients with Barrett's esophagus (BE) and cirrhosis who develop high-grade dysplasia (HGD) or

adenocarcinoma in the setting of esophageal varices present a unique therapeutic dilemma.

There is limited literature regarding the optimal management of varices prior to invasive

procedures or surgery involving the distal esophagus. We present a case of variceal

decompression with a transjugular intrahepatic portosystemic shunt (TIPS) allowing for

successful endoscopic mucosal resection (EMR) of BE with HGD overlying esophageal varices.

Neuendorf, R., Wahbeh, H., Chamine, I., Yu, J., Hutchison, K., & Oken, B. S. (2015). The effects of

mind-body interventions on sleep quality: A systematic review. *Evidence-Based Complementary

and Alternative Medicine : ECAM, 2015*, 902708.

Study Objectives. To evaluate the effect of mind-body interventions (MBI) on sleep. Methods. We

reviewed randomized controlled MBI trials on adults (through 2013) with at least one sleep

outcome measure. We searched eleven electronic databases and excluded studies on

interventions not considering mind-body medicine. Studies were categorized by type of MBI,

whether sleep was primary or secondary outcome measure and outcome type. Results. 1323

abstracts were screened, and 112 papers were included. Overall, 67 (60%) of studies reported a

beneficial effect on at least one sleep outcome measure. Of the most common interventions,

13/23 studies using meditation, 21/30 using movement MBI, and 14/25 using relaxation reported

at least some improvements in sleep. There were clear risks of bias for many studies reviewed,

especially when sleep was not the main focus. Conclusions. MBI should be considered as a

treatment option for patients with sleep disturbance. The benefit of MBI needs to be better

documented with objective outcomes as well as the mechanism of benefit elucidated. There is

some evidence that MBI have a positive benefit on sleep quality. Since sleep has a direct impact

on many other health outcomes, future MBI trials should consider including sleep outcome

measurements.

Newgard, C. D., & Lowe, R. A. (2015). Cost savings in trauma systems: The devil's in the details. *Annals of Emergency Medicine,*

Niemann, C. U., Feiner, J., Swain, S., Bunting, S., Friedman, M., Crutchfield, M., et al. (2015). Therapeutic hypothermia in deceased organ donors and kidney-graft function. *The New England Journal of Medicine, 373*(5), 405-414.

BACKGROUND: Delayed graft function, which is reported in up to 50% of kidney-transplant recipients, is associated with increased costs and diminished long-term graft function. The effect that targeted mild hypothermia in organ donors before organ recovery has on the rate of delayed graft function is unclear. METHODS: We enrolled organ donors (after declaration of death according to neurologic criteria) from two large donation service areas and randomly assigned them to one of two targeted temperature ranges: 34 to 35 degrees C (hypothermia) or 36.5 to 37.5 degrees C (normothermia). Temperature protocols, which were initiated after authorization was obtained for the organ to be donated and for the donor's participation in the study, ended when organ donors left the intensive care unit for organ recovery in the operating room. The primary outcome was delayed graft function in the kidney recipients, which was defined as the requirement for dialysis during the first week after transplantation. Secondary outcomes were the rates of individual organs transplanted in each treatment group and the total number of organs transplanted from each donor. RESULTS: The study was terminated early, on the recommendation of an independent data and safety monitoring board, after the interim analysis showed efficacy of hypothermia. At trial termination, 370 organ donors had been enrolled (180 in the hypothermia group and 190 in the normothermia group). A total of 572 patients received a kidney transplant (285 kidneys from donors in the hypothermia group and 287 kidneys from donors in the normothermia group). Delayed graft function developed in 79 recipients of kidneys from donors in the hypothermia group (28%) and in 112 recipients of kidneys from donors in the normothermia group (39%) (odds ratio, 0.62; 95% confidence interval, 0.43 to 0.92; P=0.02). CONCLUSIONS: Mild hypothermia, as compared with normothermia, in organ donors after declaration of death according to neurologic criteria significantly reduced the rate of delayed graft function among recipients. (Funded by the Health Resources and Services Administration; ClinicalTrials.gov number, NCT01680744.).

Nunez-Forero, L., Moyano-Ariza, L., Gaitan-Duarte, H., Angel-Muller, E., Ruiz-Parra, A., Gonzalez, 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 Bogota, 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.

Obregon, F., Vaquette, C., Ivanovski, S., Hutmacher, D. W., & Bertassoni, L. E. (2015). Three-

dimensional bioprinting for regenerative dentistry and craniofacial tissue engineering. *Journal of*

Dental Research,

Craniofacial tissues are organized with complex 3-dimensional (3D) architectures. Mimicking such

3D complexity and the multicellular interactions naturally occurring in craniofacial structures

represents one of the greatest challenges in regenerative dentistry. Three-dimensional bioprinting

of tissues and biological structures has been proposed as a promising alternative to address some

of these key challenges. It enables precise manufacture of various biomaterials with complex 3D

architectures, while being compatible with multiple cell sources and being customizable to patient-specific needs. This review describes different 3D bioprinting methods and summarizes how different classes of biomaterials (polymer hydrogels, ceramics, composites, and cell aggregates) may be used for 3D biomanufacturing of scaffolds, as well as craniofacial tissue analogs. While the fabrication of scaffolds upon which cells attach, migrate, and proliferate is already in use, printing of all the components that form a tissue (living cells and matrix materials together) to produce tissue constructs is still in its early stages. In summary, this review seeks to highlight some of the key advantages of 3D bioprinting technology for the regeneration of craniofacial structures. Additionally, it stimulates progress on the development of strategies that will promote the translation of craniofacial tissue engineering from the laboratory bench to the chair side.

Ogawa, M., Ogawa, S., Bear, C. E., Ahmadi, S., Chin, S., Li, B., et al. (2015). Directed differentiation of cholangiocytes from human pluripotent stem cells. *Nature Biotechnology,*
Although bile duct disorders are well-recognized causes of liver disease, the molecular and cellular events leading to biliary dysfunction are poorly understood. To enable modeling and drug discovery for biliary disease, we describe a protocol that achieves efficient differentiation of biliary epithelial cells (cholangiocytes) from human pluripotent stem cells (hPSCs) through delivery of developmentally relevant cues, including NOTCH signaling. Using three-dimensional culture, the protocol yields cystic and/or ductal structures that express mature biliary markers, including apical sodium-dependent bile acid transporter, secretin receptor, cilia and cystic fibrosis transmembrane conductance regulator (CFTR). We demonstrate that hPSC-derived cholangiocytes possess epithelial functions, including rhodamine efflux and CFTR-mediated fluid secretion. Furthermore, we show that functionally impaired hPSC-derived cholangiocytes from cystic fibrosis patients are rescued by CFTR correctors. These findings demonstrate that mature cholangiocytes can be differentiated from hPSCs and used for studies of biliary development and disease.

Okitundu Luwa E-Andjafono, D., Bumoko Makila-Mabe, G., Ayanne, M. T., Kikandau, J. K., Mashukano, N., Kazadi Kayembe, T., et al. (2014). Persistence of konzo epidemics in kahemba, democratic

republic of congo: Phenomenological and socio-economic aspects. [Persistance des epidemies de konzo a Kahemba, Republique Democratique du Congo: aspects phenomenologiques et socio-economiques] *The Pan African Medical Journal, 18*, 213.

Olson, R., Elliot, D., Hess, J., Thompson, S., Luther, K., Wipfli, B., et al. (2014). The COMmunity of practice and safety support (COMPASS) total worker health study among home care workers: Study protocol for a randomized controlled trial. *Trials, 15*, 411-6215-15-411. BACKGROUND: Home care workers are a high-risk group for injury and illness. Their unique work structure presents challenges to delivering a program to enhance their health and safety. No randomized controlled trials have assessed the impact of a Total Worker Health program designed for their needs. METHODS/DESIGN: The COMPASS (COMmunity of Practice And Safety Support) study is a cluster randomized trial being implemented among Oregon's unionized home care workers. Partnering with the Oregon Home Care Commission allowed recruiting 10 pairs of home care worker groups with 8 participants per group (n = 160) for balanced randomization of groups to intervention and control conditions. Physiologic and survey evaluation of all participants will be at enrollment, 6 months and 12 months. Primary outcomes are to increase health promoting (for example, healthy nutrition and regular physical activity) and health protecting (that is, safety) behaviors. In addition to assessing outcomes adjusted for the hierarchical design, mediation analyses will be used to deconstruct and confirm the program's theoretical underpinnings and intervention processes. Intervention groups will participate in a series of monthly 2-hour meetings designed as ritualized, scripted peer-led sessions to increase knowledge, practice skills and build support for healthy actions. Self-monitoring and individual and team level goals are included to augment change. Because generalizability, reach and achieving dissemination are priorities, following initial wave findings, a second wave of COMPASS groups will be recruited and enrolled with tailoring of the program to align with existing Home Care Commission educational offerings. Outcomes, process and mediation of those tailored groups will be compared with the original wave's findings. DISCUSSION: The COMPASS trial will assess a novel program to enhance the safety and health of a vulnerable, rapidly expanding group of isolated caregivers, whose critical work allows independent living of frail seniors and the

disabled. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT02113371, first registered 11 March 2014.

Olson, R., Elliot, D., Hess, J., Thompson, S., Luther, K., Wipfli, B., et al. (2015). The COMmunity of practice and safety support (COMPASS) total worker health™ study among home care workers: Study protocol for a randomized controlled trial. *Trials,*
Background: Home care workers are a high-risk group for injury and illness. Their unique work structure presents challenges to delivering a program to enhance their health and safety. No randomized controlled trials have assessed the impact of a Total Worker Health™ program designed for their needs. Methods/design: The COMPASS (COMmunity of Practice And Safety Support) study is a cluster randomized trial being implemented among Oregon's unionized home care workers. Partnering with the Oregon Home Care Commission allowed recruiting 10 pairs of home care worker groups with 8 participants per group (n = 160) for balanced randomization of groups to intervention and control conditions. Physiologic and survey evaluation of all participants will be at enrollment, 6 months and 12 months. Primary outcomes are to increase health promoting (for example, healthy nutrition and regular physical activity) and health protecting (that is, safety) behaviors. In addition to assessing outcomes adjusted for the hierarchical design, mediation analyses will be used to deconstruct and confirm the program's theoretical underpinnings and intervention processes. Intervention groups will participate in a series of monthly 2-hour meetings designed as ritualized, scripted peer-led sessions to increase knowledge, practice skills and build support for healthy actions. Self-monitoring and individual and team level goals are included to augment change. Because generalizability, reach and achieving dissemination are priorities, following initial wave findings, a second wave of COMPASS groups will be recruited and enrolled with tailoring of the program to align with existing Home Care Commission educational offerings. Outcomes, process and mediation of those tailored groups will be compared with the original wave's findings. Discussion: The COMPASS trial will assess a novel program to enhance the safety and health of a vulnerable, rapidly expanding group of isolated caregivers, whose critical work allows independent living of frail seniors and the disabled. Trial registration: ClinicalTrials.gov identifier: NCT02113371, first registered 11 March 2014. © 2014 Olson et al.; licensee BioMed Central Ltd.

Ostrowski, K. A., Dugi, D. D.,3rd, Hedges, J. C., & Barry, J. M. (2015). Bone saw for calcified

peyronie's disease plaques. *Urology,*

OBJECTIVES: To determine the incidence of calcified Peyronie's disease plaque that cannot be cut

with a blade in a 100-case series and to describe the use of a soft tissue-protecting bone saw for

plaque incision. METHODS: Chart reviews were done of all surgically treated Peyronie's disease

patients at our center between October 1996 and December 2012. 100 cases were included. We

evaluated our novel technique of tissue-protecting bone saw surgical use. RESULTS: 100

consecutive patients underwent surgery for Peyronie's disease, and 6 required transverse bone

saw plaque incision due to the severity of calcification that could not be cut with a blade. Four of

those 6 underwent grafting procedures with porcine submucosal intestinal substance (SIS) and 2

underwent placement of inflatable penile prosthesis (IPP) after plaque incision. There were no

surgical complications. Both IPP patients had functioning prosthesis 4 and 7.3 years after

surgery. One SIS-graft patient required re-operation for more proximal curvature 11 months

later and ultimately required multiple plaque incisions and an IPP. CONCLUSION: Densely

calcified plaques occurred in 6% of a surgical series of Peyronie's disease patients. The vibrating

bone saw is a novel technique to incise calcified plaques before grafting or IPP placement.

O'Tierney-Ginn, P., Roberts, V., Gillingham, M., Walker, J., Glazebrook, P. A., Thornburg, K. L., et al.

(2015). Influence of high fat diet and resveratrol supplementation on placental fatty acid uptake

in the japanese macaque. *Placenta,*

INTRODUCTION: Adequate maternal supply and placental delivery of long chain polyunsaturated

fatty acids (LCPUFA) is essential for normal fetal development. In humans, maternal obesity

alters placental FA uptake, though the impact of diet remains uncertain. The fatty fetal liver

observed in offspring of Japanese macaques fed a high fat diet (HFD) was prevented with

resveratrol supplementation during pregnancy. We sought to determine the effect of HFD and

resveratrol, a supplement with insulin-sensitizing properties, on placental LCPUFA uptake in this

model. METHODS: J. macaques were fed control chow (15% fat, n = 5), HFD (35% fat, n = 10)

or HFD containing 0.37% resveratrol (n = 5) prior to- and throughout pregnancy. At

approximately 130d gestation (term = 173d), placentas were collected by caesarean section.

Fatty acid uptake studies using 14C-labeled oleic acid, arachidonic acid (AA) and docosahexanoic

acid (DHA) were performed in placental explants. RESULTS: Resveratrol supplementation increased placental uptake of DHA ($P < 0.05$), while HFD alone had no measurable effect. Resveratrol increased AMP-activated protein kinase activity and mRNA expression of the fatty acid transporters FATP-4, CD36 and FABPpm ($P < 0.05$). Placental DHA content was decreased in HFD dams; resveratrol had no effect on tissue fatty acid profiles. DISCUSSION: Maternal HFD did not significantly affect placental LCPUFA uptake. Furthermore, resveratrol stimulated placental DHA uptake capacity, AMPK activation and transporter expression. Placental handling of DHA is particularly sensitive to the dramatic alterations in the maternal metabolic phenotype and placental AMPK activity associated with resveratrol supplementation.

Ozpinar, A., Magill, S. T., Davies, J. M., & McDermott, M. W. (2015). Vertebral artery fenestration. *Cureus, 7*(1), e245.

Fenestration of the vertebral artery is a rare vascular anomaly that has been observed at autopsy and on angiography. It is most commonly seen in the extracranial segments of the vertebral artery. This congenital anomaly can arise during multiple different stages of embryological development of the vertebral artery. The clinical significance is unclear, but multiple studies have reported association with other vascular anomalies. Awareness of vascular anomalies is crucial to avoid iatrogenic injuries during endovascular diagnostic and therapeutic interventions. Here, we present a case of a patient with an intracranial vertebral artery fenestration that was identified during work-up for a foramen magnum mass.

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

Pahuja, K. B., Wang, J., Blagoveshchenskaya, A., Lim, L., Madhusudhan, M. S., Mayinger, P., et al. (2015). Phosphoregulatory protein 14-3-3 facilitates SAC1 transport from the endoplasmic reticulum. *Proceedings of the National Academy of Sciences of the United States of America, 112*(25), E3199-E3206.

Most secretory cargo proteins in eukaryotes are synthesized in the endoplasmic reticulum and actively exported in membrane-bound vesicles that are formed by the cytosolic coat protein complex II (COPII). COPII proteins are assisted by a variety of cargo-specific adaptor proteins required for the concentration and export of secretory proteins from the endoplasmic reticulum

(ER). Adaptor proteins are key regulators of cargo export, and defects in their function may result in disease phenotypes in mammals. Here we report the role of 14-3-3 proteins as a cytosolic adaptor in mediating SAC1 transport in COPII-coated vesicles. Sac1 is a phosphatidyl inositol-4 phosphate (PI4P) lipid phosphatase that undergoes serum dependent translocation between the endoplasmic reticulum and Golgi complex and controls cellular PI4P lipid levels. We developed a cell-free COPII vesicle budding reaction to examine SAC1 exit from the ER that requires COPII and at least one additional cytosolic factor, the 14-3-3 protein. Recombinant 14-3-3 protein stimulates the packaging of SAC1 into COPII vesicles and the sorting subunit of COPII, Sec24, interacts with 14-3-3. We identified a minimal sorting motif of SAC1 that is important for 14-3-3 binding and which controls SAC1 export from the ER. This LS motif is part of a 7-aa stretch, RLSNTSP, which is similar to the consensus 14-3-3 binding sequence. Homology models, based on the SAC1 structure from yeast, predict this region to be in the exposed exterior of the protein. Our data suggest a model in which the 14-3-3 protein mediates SAC1 traffic from the ER through direct interaction with a sorting signal and COPII.

Paiva, C., Godbersen, J. C., Berger, A., Brown, J. R., & Danilov, A. V. (2015). Targeting neddylation induces DNA damage and checkpoint activation and sensitizes chronic lymphocytic leukemia B cells to alkylating agents. *Cell Death & Disease, 6*, e1807.

Microenvironment-mediated upregulation of the B-cell receptor (BCR) and nuclear factor-kappaB (NF-kappaB) signaling in CLL cells resident in the lymph node and bone marrow promotes apoptosis evasion and clonal expansion. We recently reported that MLN4924 (pevonedistat), an investigational agent that inhibits the NEDD8-activating enzyme (NAE), abrogates stromal-mediated NF-kappaB pathway activity and CLL cell survival. However, the NAE pathway also assists degradation of multiple other substrates. MLN4924 has been shown to induce DNA damage and cell cycle arrest, but the importance of this mechanism in primary neoplastic B cells has not been studied. Here we mimicked the lymph node microenvironment using CD40 ligand (CD40L)-expressing stroma and interleukin-21 (IL-21) to find that inducing proliferation of the primary CLL cells conferred enhanced sensitivity to NAE inhibition. Treatment of the CD40-stimulated CLL cells with MLN4924 resulted in deregulation of Cdt1, a DNA replication licensing

factor, and cell cycle inhibitors p21 and p27. This led to DNA damage, checkpoint activation and G2 arrest. Alkylating agents bendamustine and chlorambucil enhanced MLN4924-mediated DNA damage and apoptosis. These events were more prominent in cells stimulated with IL-21 compared with CD40L alone, indicating that, following NAE inhibition, the culture conditions were able to direct CLL cell fate from an NF-kappaB inhibition to a Cdt1 induction program. Our data provide insight into the biological consequences of targeting NAE in CLL and serves as further rationale for studying the clinical activity of MLN4924 in CLL, particularly in combination with alkylating agents.

Paten, B., Diekhans, M., Druker, B. J., Friend, S., Guinney, J., Gassner, N., et al. (2015). The NIH BD2K center for big data in translational genomics. *Journal of the American Medical Informatics Association : JAMIA,*

The world's genomics data will never be stored in a single repository - rather, it will be distributed among many sites in many countries. No one site will have enough data to explain genotype to phenotype relationships in rare diseases; therefore, sites must share data. To accomplish this, the genetics community must forge common standards and protocols to make sharing and computing data among many sites a seamless activity. Through the Global Alliance for Genomics and Health, we are pioneering the development of shared application programming interfaces (APIs) to connect the world's genome repositories. In parallel, we are developing an open source software stack (ADAM) that uses these APIs. This combination will create a cohesive genome informatics ecosystem. Using containers, we are facilitating the deployment of this software in a diverse array of environments. Through benchmarking efforts and big data driver projects, we are ensuring ADAM's performance and utility.

Petersen, J., Thielke, S., Austin, D., & Kaye, J. (2015). Phone behaviour and its relationship to loneliness in older adults. *Aging & Mental Health,* , 1-8.

OBJECTIVES: Loneliness and social isolation are two important health outcomes among older adults. Current assessment of these outcomes relies on self-report which is susceptible to bias. This paper reports on the relationship between loneliness and objective measures of isolation using a phone monitoring device. METHOD: Phone monitors were installed in the homes of 26

independent elderly individuals from the ORCATECH Life Laboratory cohort (age 86 +/- 4.5, 88% female) and used to monitor the daily phone usage for an average of 174 days. Loneliness was assessed using the 20-item University of California Los Angeles (UCLA) Loneliness scale. A mixed effects negative binomial regression was used to model the relationship between loneliness and social isolation, as assessed using the total number of calls, controlling for cognitive function, pain, age, gender, and weekday. A secondary analysis examined the differential effect of loneliness on incoming and outgoing calls. RESULTS: The average UCLA Loneliness score was 35.3 +/- 7.6, and the median daily number of calls was 4. Loneliness was negatively associated with telephone use (IRR = 0.99, p < 0.05). Daily phone use was also associated with gender (IRR = 2.03, p < 0.001) and cognitive status (IRR = 1.51, p < 0.001). The secondary analysis revealed that loneliness was significantly related to incoming (IRR = 0.98, p < 0.01) but not outgoing calls. CONCLUSIONS: These results demonstrate the close relationship between loneliness and social isolation, showing that phone behaviour is associated with emotional state and cognitive function. Because phone behaviour can be monitored unobtrusively, it may be possible to sense loneliness levels in older adults using objective assessments of key aspects of behaviour.

Platt, E. J., Durnin, J. P., & Kabat, D. (2015). HIV-1 variants that use mouse CCR5 reveal critical interactions of gp120's V3 crown with CCR5 extracellular loop 1. *AIDS Research and Human Retroviruses,*

The CCR5 coreceptor amino terminus and extracellular (ECL) loops 1 and 2 have been implicated in HIV-1 infections, with species differences in these regions inhibiting zoonoses. Interactions of gp120 with CD4 and CCR5 reduce constraints on metastable envelope subunit gp41, enabling gp41 conformational changes needed for infection. We previously selected HIV-1JRCSF variants that efficiently use CCR5(Delta18) with a deleted amino terminus or CCR5(HHMH) with ECL2 from an NIH/Swiss mouse. Unexpectedly, the adaptive gp120 mutations were nearly identical, suggesting that they function by weakening gp120's grip on gp41 and/or by increasing interactions with ECL1. To analyze this and further wean HIV-1 from human CCR5, we selected variants using CCR5(HMMH) with murine ECL1 and 2 sequences. HIV-1JRCSF mutations adaptive for CCR5(Delta18) and CCR5(HHMH) were generally maladaptive for CCR5(HMMH), whereas the

converse was true for CCR5(HMMH) adaptations. The HIV-1JRCSF variant adapted to CCR5(HMMH) also weakly used intact NIH/Swiss mouse CCR5. Our results strongly suggest that HIV-1JRCSF makes functionally critical contacts with human ECL1 and that adaptation to murine ECL1 requires multiple mutations in the crown of gp120's V3 loop.

Poetker, D. M., & Smith, T. L. (2015). Medicolegal implications of common rhinologic medications. *Otolaryngologic Clinics of North America,*

As otolaryngologists, we prescribe many medications to our patients. The objective of this article is to review the potential side effects and medicolegal risks of the common medications used to treat chronic rhinosinusitis. The authors evaluate some of the common side effects as well as the published literature on the lawsuits associated with those medications. Finally, the authors review the informed consent discussion and opportunities to improve patient care and decrease the risk of litigation.

Pommerening, M. J., Rahbar, E., Minei, K., Holcomb, J. B., Wade, C. E., Schreiber, M. A., et al. (2015). Splenectomy is associated with hypercoagulable thrombelastography values and increased risk of thromboembolism. *Surgery,*

BACKGROUND: Previous investigators have demonstrated that postinjury thrombocytosis is associated with an increase in thromboembolic (TE) risk. Increased rates of thrombocytosis have been found specifically in patients after splenectomy for trauma. We hypothesized that patients undergoing splenectomy (1) would demonstrate a more hypercoagulable profile during their hospital stay and (2) that this hypercoagulable state would be associated with increased TE events. METHODS: This was a 14-month, prospective, observational trial evaluating serial rapid thrombelastography (rTEG) at 3 American College of Surgeons-verified, level 1 trauma centers. Inclusion criteria were highest-level trauma activation and arrival within 6 hours of injury. Exclusion criteria were 20% total body surface area. Serial rTEG (activated clotting time, k-time, alpha-angle, MA, lysis) and traditional coagulation testing (prothrombin time, partial thromboplastin time, fibrinogen and platelet count) were obtained at admission and then at 3, 6, 12, 24, 48, 72, 96, and 120 hours. Thromboembolic complications were defined as the development of deep-vein thrombosis, pulmonary embolism, acute myocardial infarction, or

ischemic stroke during hospitalization. Patients were stratified into splenectomy versus nonsplenectomy cohorts. Univariate analysis was then conducted followed by longitudinal analysis using generalized estimating equations to evaluate the effects of time, splenectomy, and group-time interactions on changes in rTEG and traditional coagulation testing. We used an adjusted generalized estimating equation model to control for age, sex, ISS, admission blood pressure, base deficit, and hemoglobin. RESULTS: A total of 1,242 patients were enrolled; 795 had serial rTEG data. Of these, 605 had serial values >24 hours and made up the study population. Splenectomy patients were younger, more hypotensive, and in shock on arrival. Although there was no difference in 24-hour or 30-day mortality, splenectomy patients were more likely to develop TE events. Using the GEE model, we found that alpha-angle and MA in splenectomy patients were lesser (more hypocoagulable) within the first 6 hours; however, they became substantially greater (more hypercoagulable) at 48, 72, 96, and 120 hours; all P < .05. In addition, platelet counts were greater in the splenectomy group beginning at 72 hours and continuing through 120 hours; P < .05. CONCLUSION: This multicenter, prospective study demonstrates that patients undergoing splenectomy have a more hypercoagulable state than other trauma patients. This hypercoagulable state (identified by greater alpha-angle and mA values) begins at approximately 48 hours after injury and continues through at least day 5. Moreover, this hypercoagulable state is associated with increased risk of TE complications.

Predazzi, I. M., Sobota, R. S., Sanna, S., Bush, W. S., Bartlett, J., Lilley, J. S., et al. (2015). Sex-specific parental effects on offspring lipid levels. *Journal of the American Heart Association, 4*(7), 10.1161/JAHA.115.001951.

BACKGROUND: Plasma lipid levels are highly heritable traits, but known genetic loci can only explain a small portion of their heritability. METHODS AND RESULTS: In this study, we analyzed the role of parental levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) in explaining the values of the corresponding traits in adult offspring. We also evaluated the contribution of nongenetic factors that influence lipid traits (age, body mass index, smoking, medications, and menopause) alone and in combination with variability at the genetic loci known to associate with TC, LDL-C, HDL-C, and TG levels. We performed comparisons among different sex-specific regression models

in 416 families from the Framingham Heart Study and 304 from the SardiNIA cohort. Models including parental lipid levels explain significantly more of the trait variation than models without these measures, explaining up to approximately 39% of the total trait variation. Of this variation, the parent-of-origin effect explains as much as approximately 15% and it does so in a sex-specific way. This observation is not owing to shared environment, given that spouse-pair correlations were negligible (<1.5% explained variation in all cases) and is distinct from previous genetic and acquired factors that are known to influence serum lipid levels. CONCLUSIONS: These findings support the concept that unknown genetic and epigenetic contributors are responsible for most of the heritable component of the plasma lipid phenotype, and that, at present, the clinical utility of knowing age-matched parental lipid levels in assessing risk of dyslipidemia supersedes individual locus effects. Our results support the clinical utility of knowing parental lipid levels in assessing future risk of dyslipidemia.

Price, R. B., Ferracane, J. L., & Shortall, A. C. (2015). Light-curing units: A review of what we need to know. *Journal of Dental Research,*

For improved interstudy reproducibility, reduced risk of premature failures, and ultimately better patient care, researchers and dentists need to know how to accurately characterize the electromagnetic radiation (light) they are delivering to the resins they are using. The output from a light-curing unit (LCU) is commonly characterized by its irradiance. If this value is measured at the light tip, it describes the radiant exitance from the surface of the light tip, and not the irradiance received by the specimen. The value quoted also reflects only an averaged value over the total measurement area and does not represent the irradiance that the resin specimen is receiving locally or at a different moment in time. Recent evidence has reported that the spectral emission and radiant exitance beam profiles from LCUs can be highly inhomogeneous. This can cause nonuniform temperature changes and uneven photopolymerization within the resin restoration. The spectral radiant power can be very different between different brands of LCUs, and the use of irradiance values derived from dental radiometers to describe the output from an LCU for research purposes is discouraged. Manufacturers should provide more information about the light output from the LCU and the absorption spectrum of their resin-based composite (RBC). Ideally, future assessments and research publications should include the following information

about the curing light: 1) radiant power output throughout the exposure cycle and the spectral radiant power as a function of wavelength, 2) analysis of the light beam profile and spectral emission across the light beam, and 3) measurement and reporting of the light the RBC specimen received as well as the output measured at the light tip.

Pritham Raj, Y. (2015). Establish the cause, employ a multifactorial approach. *Current Psychiatry, 14*(3), 19-21 and 28-31.

Quezada, E., Lapidus, J., Shaughnessy, R., Chen, Z., & Silberbach, M. (2015). Aortic dimensions in turner syndrome. *American Journal of Medical Genetics.Part A,*
In Turner syndrome, linear growth is less than the general population. Consequently, to assess stature in Turner syndrome, condition-specific comparators have been employed. Similar reference curves for cardiac structures in Turner syndrome are currently unavailable. Accurate assessment of the aorta is particularly critical in Turner syndrome because aortic dissection and rupture occur more frequently than in the general population. Furthermore, comparisons to references calculated from the taller general population with the shorter Turner syndrome population can lead to over-estimation of aortic size causing stigmatization, medicalization, and potentially over-treatment. We used echocardiography to measure aortic diameters at eight levels of the thoracic aorta in 481 healthy girls and women with Turner syndrome who ranged in age from two to seventy years. Univariate and multivariate linear regression analyses were performed to assess the influence of karyotype, age, body mass index, bicuspid aortic valve, blood pressure, history of renal disease, thyroid disease, or growth hormone therapy. Because only bicuspid aortic valve was found to independently affect aortic size, subjects with bicuspid aortic valve were excluded from the analysis. Regression equations for aortic diameters were calculated and Z-scores corresponding to 1, 2, and 3 standard deviations from the mean were plotted against body surface area. The information presented here will allow clinicians and other caregivers to calculate aortic Z-scores using a Turner-based reference population. (c) 2015 Wiley Periodicals, Inc.

Rab, T., Kern, K. B., Tamis-Holland, J. E., Henry, T. D., McDaniel, M., Dickert, N. W., et al. (2015). Cardiac arrest: A treatment algorithm for emergent invasive cardiac procedures in the

resuscitated comatose patient. *Journal of the American College of Cardiology, 66*(1), 62-73. Patients who are comatose after cardiac arrest continue to be a challenge, with high mortality. Although there is an American College of Cardiology Foundation/American Heart Association Class I recommendation for performing immediate angiography and percutaneous coronary intervention (when indicated) in patients with ST-segment elevation myocardial infarction, no guidelines exist for patients without ST-segment elevation. Early introduction of mild therapeutic hypothermia is an established treatment goal. However, there are no established guidelines for risk stratification of patients for cardiac catheterization and possible percutaneous coronary intervention, particularly in patients who have unfavorable clinical features in whom procedures may be futile and affect public reporting of mortality. An algorithm is presented to improve the risk stratification of these severely ill patients with an emphasis on consultation and evaluation of patients prior to activation of the cardiac catheterization laboratory.

Raber, J., Marzulla, T., Stewart, B., Kronenberg, A., & Turker, M. S. (2015). 28Silicon irradiation impairs contextual fear memory in B6D2F1 mice. *Radiation Research, 183*(6), 708-712. The space radiation environment consists of multiple species of charged particles, including 28Si, 48Ti and protons that may impact cognition, but their damaging effects have been poorly defined. In mouse studies, C57Bl6/J homozygous wild-type mice and genetic mutant mice on a C57Bl6/J background have typically been used for assessing effects of space radiation on cognition. In contrast, little is known about the radiation response of mice on a heterozygous background. Therefore, in the current study we tested the effects of 28Si, 48Ti and proton radiation on hippocampus-dependent contextual fear memory and hippocampus-independent cued fear memory in C57Bl6/J × DBA2/J F1 (B6D2F1) mice three months after irradiation. Contextual fear memory was impaired at a 1.6 Gy dose of 28Si radiation, but not cued fear memory. 48Ti or proton irradiation did not affect either type of memory. Based on earlier space radiation cognitive data in C57Bl6/J mice, these data highlight the importance of including different genetic backgrounds in studies aimed at assessing cognitive changes after exposure to space radiation. © 2015 by Radiation Research Society.

Ramachandran, D., Zeng, Z., Locke, A. E., Mulle, J. G., Bean, L. J., Rosser, T. C., et al. (2015).

Genome-wide association study of down syndrome-associated atrioventricular septal defects. *G3 (Bethesda, Md.),*

The goal of this study was to identify the contribution of common genetic variants to Down syndrome-associated atrioventricular septal defect, a severe heart abnormality. Compared to the euploid population, infants with Down syndrome, or trisomy 21, have a 2000-fold increased risk of presenting with atrioventricular septal defects. The cause of this elevated risk remains elusive. Here we present data from the largest heart study conducted to date on a trisomic background using a carefully characterized collection of individuals from extreme ends of the phenotypic spectrum. We performed a genome-wide association study using logistic regression analysis on 452 individuals with Down syndrome, consisting of 210 cases with complete atrioventricular septal defects and 242 controls with structurally normal hearts. No individual variant achieved genome-wide significance. We identified four disomic regions (1p36.3, 5p15.31, 8q22.3, and 17q22) and two trisomic regions on chromosome 21 (around PDXK and KCNJ6 genes) that merit further investigation in large replication studies. Our data show that a few common genetic variants of large effect size (odds ratio > 2.0) do not account for the elevated risk of Down syndrome-associated atrioventricular septal defects. Instead, multiple variants of low-to-moderate effect sizes may contribute to this elevated risk, highlighting the complex genetic architecture of atrioventricular septal defects even in the highly susceptible Down syndrome population.

Ramanathan, R. K., McDonough, S. L., Kennecke, H. F., Iqbal, S., Baranda, J. C., Seery, T. E., et al. (2015). Phase 2 study of MK-2206, an allosteric inhibitor of AKT, as second-line therapy for advanced gastric and gastroesophageal junction cancer: A SWOG cooperative group trial (S1005). *Cancer, 121*(13), 2193-2197.

BACKGROUND The AKT inhibitor MK-2206 at a dose of 60 mg every other day was evaluated in gastric/gastroesophageal junction cancers. METHODS Patients who had progressed after first-line treatment were eligible. Pertinent eligibility criteria included adequate organ function, a fasting serum glucose level ≤ 150 mg/dL, and less than grade 2 malabsorption or chronic diarrhea. MK-2206 was given orally (60 evaluable patients required). The primary endpoint was overall

survival, and a median survival of 6.5 months (power, 89%; significance level, 0.07) was considered encouraging for further investigation. RESULTS Seventy patients were included in the final analyses. The median age was 59.8 years (range, 30.4-86.7 years); 70% were male, 89% were white, and 7% were Asian. There were 2 deaths possibly related to the study drug (cardiac arrest and respiratory failure). Grade 4 adverse events included hyperglycemia, anemia, and lung infection (1 each). Grade 3 adverse events occurred in < 5% of patients except for fatigue (6%). Other adverse events (all grades) included anemia (17%), anorexia (30%), diarrhea (26%), fatigue (50%), hyperglycemia (30%), nausea (40%), vomiting (22%), dry skin (19%), maculopapular rash (30%), and acneiform rash (13%). The response rate was 1%, the median progression-free survival was 1.8 months (95% confidence interval, 1.7-1.8 months), and the median overall survival was 5.1 months (95% confidence interval, 3.7-9.4 months) CONCLUSIONS MK-2206 as second-line therapy was well tolerated by an unselected group of patients with gastric/gastroesophageal junction cancers, but it did not have sufficient activity (response rate, 1%; overall survival, 5.1 months) to warrant further testing in this population. Cancer 2015;121:2193-2197. © 2015 American Cancer Society.

Reddy, U. M., Rice, M. M., Grobman, W. A., Bailit, J. L., Wapner, R. J., Varner, M. W., et al. (2015). Serious maternal complications after early preterm delivery (24-33 weeks' gestation). *American Journal of Obstetrics and Gynecology,*

OBJECTIVE: We sought to describe the prevalence of serious maternal complications following early preterm birth by gestational age (GA), delivery route, and type of cesarean incision. STUDY DESIGN: Trained personnel abstracted data from maternal and neonatal charts for all deliveries on randomly selected days representing one third of deliveries across 25 US hospitals over 3 years (n = 115,502). All women delivering nonanomalous singletons between 23-33 weeks' gestation were included. Women were excluded for antepartum stillbirth and highly morbid conditions for which route of delivery would not likely impact morbidity including nonreassuring fetal status, cord prolapse, placenta previa, placenta accreta, placental abruption, and severe and unstable maternal conditions (cardiopulmonary collapse, acute respiratory distress syndrome, seizures). Serious maternal complications were defined as: hemorrhage (blood loss >/=1500 mL, blood transfusion, or hysterectomy for hemorrhage), infection (endometritis, wound dehiscence,

or wound infection requiring antibiotics, reopening, or unexpected procedure), intensive care unit admission, or death. Delivery route was categorized as classic cesarean delivery (CCD), low transverse cesarean delivery (LTCD), low vertical cesarean delivery (LVCD), and vaginal delivery. Association of delivery route with complications was estimated using multivariable regression models yielding adjusted relative risks (aRR) controlling for maternal age, race, body mass index, hypertension, diabetes, preterm premature rupture of membranes, preterm labor, GA, and hospital of delivery. RESULTS: Of 2659 women who met criteria for inclusion in this analysis, 8.6% of women experienced serious maternal complications. Complications were associated with GA and were highest between 23-27 weeks of gestation. The frequency of complications was associated with delivery route; compared with 3.5% of vaginal delivery, 23.0% of CCD (aRR, 3.54; 95% confidence interval (CI), 2.29-5.48), 12.1% of LTCD (aRR, 2.59; 95% CI, 1.77-3.77), and 10.3% of LVCD (aRR, 2.27; 95% CI, 0.68-7.55) experienced complications. There was no significant difference in complication rates between CCD and LTCD (aRR, 1.37; 95% CI, 0.95-1.97) or between CCD and LVCD (aRR, 1.56; 95% CI, 0.48-5.07). CONCLUSION: The risk of maternal complications after early preterm delivery is substantial, particularly in women who undergo cesarean delivery. Obstetricians need to be prepared to manage potential hemorrhage, infection, and intensive care unit admission for early preterm births requiring cesarean delivery.

Reschke, L. D., Miller, E. R.,3rd, Fadrowski, J. J., Loeffler, L. F., Holmes, K. W., Appel, L. J., et al. (2015). Elevated uric acid and obesity-related cardiovascular disease risk factors among hypertensive youth. *Pediatric Nephrology (Berlin, Germany),*

BACKGROUND: Uric acid (UA) is associated with high blood pressure in adolescents and with left ventricular hypertrophy (LVH) and cardiovascular disease (CVD) in adults. We sought to determine if UA is independently associated with CVD risk factors and left ventricular mass (LVM) over time in hypertensive youth. METHODS: This was a 1-year prospective observational study of hypertensive children aged 3-19 years. Cross-sectional and longitudinal associations of serum UA with CVD risk factors and LVM were explored. RESULTS: Of the 49 children who completed both the baseline and 12-month assessments, at baseline the mean age was 13.8 years and mean UA was 5.5 mg/dL; 24 % had elevated UA, 51 % were overweight/obese and 39 % had LVH. Measures of adiposity, low high-density lipoprotein cholesterol, high-sensitivity C-reactive

protein, LVM and LVH were all significantly associated with elevated UA at baseline, but not with change over time. Each 1 mg/dL increase in baseline UA was associated with a 2.5 g/m2.7 increase in the LVM index at follow-up (95 % confidence interval 0.64, 4.39; p = 0.01); after adjustment for age, sex, race, body mass index z-score, change in UA, time, blood pressure and medication use, this association was no longer significant. CONCLUSIONS: Hypertensive children with elevated UA have a higher prevalence of obesity-related CVD risk factors. Among hypertensive children, UA may be a marker of adiposity and not an independent CVD risk factor.

Ricardo, A. C., Athavale, A., Chen, J., Hampole, H., Garside, D., Marucha, P., et al. (2015). Periodontal disease, chronic kidney disease and mortality: Results from the third national health and nutrition examination survey. *BMC Nephrology, 16*, 97-015-0101-x. BACKGROUND: Periodontal disease is associated with increased mortality in the general population, however its prognostic significance in chronic kidney disease (CKD) is not known. We evaluated the joint effect of periodontal disease and CKD on all-cause and cardiovascular mortality. METHODS: Prospective observational study of 10,755 adult participants in the National Health and Nutrition Examination Survey, 1988-1994 (NHANES III). CKD was defined as estimated glomerular filtration rate /= 30 mg/g. Periodontal disease was defined as moderate (> 4 mm attachment loss in >/= 2 mesial sites or 5 mm pocket depth in >/= 2 mesial sites), or severe (> 6 mm attachment loss in >/= 2 mesial sites and > 5 mm pocket depth in >/= 1 mesial site). All-cause and cardiovascular mortality were evaluated using Cox proportional hazards models. RESULTS: There were 1,813 deaths over a median follow-up of 14 years. In multivariate analyses, as compared to participants with neither periodontal disease nor CKD, those with periodontal disease only or CKD only had increased all-cause mortality (HR 1.39; 95 % CI, 1.06 - 1.81 and 1.55; 1.30 - 1.84, respectively). The presence of both periodontal disease and CKD was associated with HR (95 % CI) 2.07 (1.65 - 2.59) for all-cause mortality, and 2.11 (1.52 - 2.94) for cardiovascular mortality. We found no evidence of multiplicativity or additivity between periodontal disease and CKD. In stratified analyses limited to individuals with CKD, periodontal disease (vs. not) was associated with adjusted HR (95 % CI) 1.35 (1.04 - 1.76) for all-cause, and 1.36 (0.95 - 1.95) for cardiovascular mortality. CONCLUSIONS: These findings confirm the well-

established association between periodontal disease and increased mortality in the general

population, and provide new evidence of this association among individuals with CKD.

Rios, H. F., Bashutski, J. D., McAllister, B. S., Murakami, S., Cobb, C. M., Chun, Y. P., et al. (2015).

Emerging regenerative approaches for periodontal reconstruction: Practical applications from the

AAP regeneration workshop. *Clinical Advances in Periodontics, 5*(1), 40-46.

FOCUSED CLINICAL QUESTION: Can emerging technologies for periodontal regeneration become

clinical reality? SUMMARY: Emerging technologies are presenting options to hopefully improve the

outcomes of regeneration in challenging clinical scenarios. Cellular allografts represent a current

technology in which cells and scaffolds are being delivered directly to the periodontal lesion.

Recombinant human fibroblast growth factor 2 and teriparatide (parathyroid 1-34) have each

been tested in controlled prospective human randomized clinical trials, and both have been

shown to have potential for periodontal regeneration. These examples, as well as other emerging

technologies, show promise for continued advancement in the field of periodontal regenerative

therapy. CONCLUSIONS: At present, there are indications that emerging technologies can be

used successfully for periodontal regeneration. Case reports and clinical trials are being

conducted with a variety of emerging technologies. However, many are yet to be approved by a

regulatory agency, or there is a lack of evidence-based literature to validate their expanded use.

Roberts, K., Simpson, M., Demner-Fushman, D., Voorhees, E., & Hersh, W. (2015). State-of-the-art in

biomedical literature retrieval for clinical cases: A survey of the TREC 2014 CDS track.

Information Retrieval,

Providing access to relevant biomedical literature in a clinical setting has the potential to bridge a

critical gap in evidence-based medicine. Here, our goal is specifically to provide relevant articles

to clinicians to improve their decision-making in diagnosing, treating, and testing patients. To this

end, the TREC 2014 Clinical Decision Support Track evaluated a system's ability to retrieve

relevant articles in one of three categories (Diagnosis, Treatment, Test) using an idealized form

of a patient medical record. Over 100 submissions from over 25 participants were evaluated on

30 topics, resulting in over 37k relevance judgments. In this article, we provide an overview of

the task, a survey of the information retrieval methods employed by the participants, an analysis

of the results, and a discussion on the future directions for this challenging yet important task. ©
2015 Springer Science+Business Media New York (outside the USA)

Rodriguez, M. I., Chang, R., & De Bocanegra, H. T. (2015). The impact of postpartum contraception
on reducing preterm birth: Findings from california. *American Journal of Obstetrics and
Gynecology,*

OBJECTIVE: Family planning is recommended as a strategy to prevent adverse birth outcomes.
The potential contribution of postpartum contraceptive coverage to reducing rates of preterm
birth is unknown. In this study, we examine the impact of contraceptive coverage and use within
18 months of a birth on preventing preterm birth in a Californian cohort. STUDY DESIGN: We
identified records for second or higher order births among women from California's 2011 Birth
Statistical Master File and their prior births from earlier Birth Statistical Master Files. To identify
women who received contraceptive services from publicly funded programs, we applied a
probabilistic linking methodology to match birth files with enrollment records for women with
Medi-Cal or Family PACT program claims. The length of contraceptive coverage was determined
through applying an algorithm based on the specified method and the quantity dispensed.
Preterm birth was defined as a birth occurring before 37 weeks gestation, and calculated from the
medical record. We further examined differences in preterm birth using subcategories defined by
the World Health Organization: extremely preterm (<28 weeks); very preterm (28 to <32
weeks); and moderate to late preterm (32 to <37 weeks). We built a multivariable regression
model to examine the effect of contraceptive coverage on the odds of a preterm birth and control
for key covariates. RESULTS: The cohort consisted of 111,948 women who were seen at least
once by a Medi-Cal or Family PACT provider within 18 months of delivery. Of the cohort, 9.75%
had a preterm birth. Contraceptive coverage was found to be protective against preterm birth.
For every month of contraceptive coverage, odds of a preterm birth less than 37 weeks decrease
by 1.1% (OR 0.989, 95% CI 0.986-0.993). CONCLUSION: Improving postpartum contraceptive
use has the potential to reduce preterm births.

Rojnueangnit, K., Xie, J., Gomes, A., Sharp, A., Callens, T., Chen, Y., et al. (2015). High incidence of
noonan syndrome features including short stature and pulmonic stenosis in patients carrying NF1

missense mutations affecting p.Arg1809: Genotype-phenotype correlation. *Human Mutation,*

Neurofibromatosis type 1 (NF1) is one of the most frequent genetic disorders, affecting 1:3000 worldwide. Identification of genotype-phenotype correlations is challenging due to the wide range clinical variability, the progressive nature of the disorder and extreme diversity of the mutational spectrum. We report 136 individuals with a distinct phenotype carrying one of 5 different NF1 missense mutations affecting p.Arg1809. Patients presented with multiple cafe-au-lait macules (CALM) with or without freckling and Lisch nodules, but no externally visible plexiform neurofibromas or clear cutaneous neurofibromas were found. About 25% of the individuals had Noonan-like features. Pulmonic stenosis and short stature were significantly more prevalent compared to classic cohorts ($p<0.0001$). Developmental delays and/or learning disabilities were reported in over 50% of patients. Melanocytes cultured from a CALM in a segmental NF1-patient showed two different somatic NF1 mutations, p.Arg1809Cys and a multi-exon deletion, providing genetic evidence that p.Arg1809Cys is a loss-of-function mutation in the melanocytes and causes a pigmentary phenotype. Constitutional missense mutations at p.Arg1809 affect 1.23% of unrelated NF1 probands in the UAB cohort, therefore this specific NF1 genotype-phenotype correlation will affect counseling and management of a significant number of patients.

Romain, A. M., Muench, J., & Phillips, J. P. (2015). Preparing family physicians for the care of patients with severe and persistent mental illness: Examples from two U.S. residency programs. *International Journal of Psychiatry in Medicine,*

Individuals with severe and persistent mental illness have increased morbidity and mortality and significant barriers to accessing health care. Although primary care providers deliver most health care for this population, residency training programs generally lack specialized training in this area. This article describes the approaches of two family medicine residency programs in addressing this educational gap. Each program collaborated with external organizations to create service models that would enhance patient access, while immersing residents in the care of patients with severe and persistent mental illness. Residents educated in these programs gain experience with an underserved population, practice advanced skills in managing complex medical and psychiatric illness, and increase knowledge from collaborative work in unique care

settings. Further implementation of programs like these, and rigorous study of such programs, could have significant benefits for family medicine education and the care of patients with severe and persistent mental illness.

Rosenbaum, J. T., Choi, D., Wilson, D. J., Grossniklaus, H. E., Harrington, C. A., Sibley, C. H., et al. (2015). Orbital pseudotumor can be a localized form of granulomatosis with polyangiitis as revealed by gene expression profiling. *Experimental and Molecular Pathology, 99*(2), 271-278. Biopsies and ANCA testing for limited forms of granulomatosis with polyangiitis (GPA) are frequently non-diagnostic. We characterized gene expression in GPA and other causes of orbital inflammation. We tested the hypothesis that a sub-set of patients with non-specific orbital inflammation (NSOI, also known as pseudotumor) mimics a limited form of GPA. Formalin-fixed, paraffin-embedded orbital biopsies were obtained from controls (n=20) and patients with GPA (n=6), NSOI (n=25), sarcoidosis (n=7), or thyroid eye disease (TED) (n=20) and were divided into discovery and validation sets. Transcripts in the tissues were quantified using Affymetrix U133 Plus 2.0 microarrays. Distinct gene expression profiles for controls and subjects with GPA, TED, or sarcoidosis were evident by principal coordinate analyses. Compared with healthy controls, 285 probe sets had elevated signals in subjects with GPA and 1472 were decreased (>1.5-fold difference, false discovery rate adjusted p<0.05). The immunoglobulin family of genes had the most dramatic increase in expression. Although gene expression in GPA could be readily distinguished from gene expression in TED, sarcoidosis, or controls, a comparison of gene expression in GPA versus NSOI found no statistically significant differences. Thus, forms of orbital inflammation can be distinguished based on gene expression. NSOI/pseudotumor is heterogeneous but often may be an unrecognized, localized form of GPA.

Rosenfeld, A. G., Knight, E. P., Steffen, A., Burke, L., Daya, M., & DeVon, H. A. (2015). Symptom clusters in patients presenting to the emergency department with possible acute coronary syndrome differ by sex, age, and discharge diagnosis. *Heart & Lung : The Journal of Critical Care,* OBJECTIVES: To identify classes of individuals presenting to the ED for suspected ACS who shared similar symptoms and clinical characteristics. BACKGROUND: Describing symptom clusters in undiagnosed patients with suspected ACS is a novel and clinically relevant approach, reflecting

real-world emergency department evaluation procedures. METHODS: Symptoms were measured using a validated 13-item symptom checklist. Latent class analysis was used to describe symptom clusters. RESULTS: The sample of 874 was 37% female with a mean age of 59.9 years. Four symptom classes were identified: Heavy Symptom Burden (Class 1), Chest Symptoms and Shortness of Breath (Class 2), Chest Symptoms Only (Class 3), and Weary (Class 4). Patients with ACS were more likely to cluster in Classes 2 and 3. Women and younger patients were more likely to group in Class 1. CONCLUSIONS: Further research is needed to determine the value of symptom clusters in the ED triage and management of suspected ACS.

Rudmik, L., Soler, Z. M., Mace, J. C., Deconde, A. S., Schlosser, R. J., & Smith, T. L. (2014). Using preoperative SNOT-22 score to inform patient decision for endoscopic sinus surgery. *Laryngoscope, 125*(7), 1517-1522.

Objectives/Hypothesis The purpose of this study is to improve patient understanding of surgical outcomes while they make a preference-sensitive decision regarding electing endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS). Study Design Prospective observational cohort study. Methods Patients with CRS who elected ESS were prospectively enrolled into a multi-institutional, observational cohort study. Patients' were categorized into 10 preoperative Sino-Nasal Outcome Test (SNOT-22) groups based on 10-point increments beginning with a score of 10 and ending at 110. The proportion of patients achieving a SNOT-22 minimal clinically important difference (MCID) (9 points) and the percentage of relative improvement (%) for each preoperative SNOT-22 group were calculated. A subgroup analysis based on polyp status was performed. Results A total of 327 patients were included in this study. Patients with a SNOT-22 score between 10 and 19 had the lowest chance of achieving an MCID (37.5%) and received a relative mean worsening of their quality of life (QoL) after ESS (+18.8%). Patients with a SNOT-22 score greater than 30 obtained a greater than 75% chance of achieving an MCID, and there was a relative improvement of 45% in QoL (all < -44.9%) after ESS. Outcomes from the polyp status subgroup analysis were similar to the findings from the overall cohort. Conclusion Outcomes from this study suggest that patients with a preoperative SNOT-22 score higher than 30 points receive a greater than 75% chance of achieving an MCID and on average obtain a 45% relative improvement in their QoL after ESS. Patients with SNOT-22 score of less than 20 did not

experience improved QoL from ESS. Level of Evidence 2b. Laryngoscope, 125:1517-1522, 2015

© 2014 The American Laryngological, Rhinological and Otological Society, Inc.

Saunders, G. H., Frederick, M. T., Arnold, M., Silverman, S., Chisolm, T. H., & Myers, P. (2015).

Auditory difficulties in blast-exposed veterans with clinically normal hearing. *Journal of*

Rehabilitation Research and Development, 52(3), 343-360.

Vast numbers of blast-injured Operation Iraqi Freedom/Operation Enduring Freedom/Operation

New Dawn personnel report postconcussive symptoms that include headache, dizziness, poor

memory, and difficulty concentrating. In addition, many report hearing problems, such as

difficulty understanding speech in noise, yet have no measureable peripheral auditory deficits. In

this article, self-report and performance-based measures were used to assess 99 blast-exposed

Veterans. All participants reported auditory problems in difficult listening situations but had

clinically normal hearing. Participants' scores on self-report questionnaires of auditory difficulties

were more similar to scores of older individuals with hearing impairment than to those of younger

individuals with normal hearing. Participants showed deficits relative to published normative data

on a number of performance-based tests that have demonstrated sensitivity to auditory

processing deficits. There were several measures on which more than the expected number of

participants (15.9%) performed one or more standard deviations below the mean. These were

assessments of speech understanding in noise, binaural processing, temporal resolution, and

speech segregation. Performance was not universally poor, with approximately 53% of

participants performing abnormally on between 3 and 6 of the 10 measures. We concluded that

participants exhibited task-specific deficits that add to the evidence suggesting that blast injury

results in damage to the central auditory system. © 2015, Rehabilitation Research and

Development Service. All rights reserved.

Scheer, J. K., Mundis, G. M., Klineberg, E., Hart, R. A., Deviren, V., Nguyen, S., et al. (2015). Post-

operative recovery following adult spinal deformity surgery: Comparative analysis of age in 149

patients during 2 year follow up. *Spine,*

STRUCTURED ABSTRACT: Study Design. Retrospective review of a multicenter, prospective adult

spinal deformity (ASD) databaseObjective. We hypothesized that increased age and increased

pre-operative disability would negatively impact both the length of time needed to achieve maximal recovery and the amount of functional improvement achieved. In order to gauge the recovery process, a normalization process was used to calculate an integrated health state (IHS) over the 2-year post-operative period. SUMMARY OF BACKGROUND DATA: Elderly ASD patients generally have worse baseline health-related quality of life (HRQOL) measures than younger patients. Current methods of reporting outcomes are limited perhaps diminishing the health impact of the entire postoperative recovery experience. METHODS: Inclusion criteria included >/=18yrs and ASD. Patient groups: young (/=65) as well as by baseline Oswestry Disability Index (ODI) scores: MILD (0-30), MEDIUM (31-49), and HIGH (>/=50). Collected HRQOL measures included ODI, Short Form-36(PCS/MCS), and Scoliosis Research Society-22 (SRS22) at baseline, 6wks, 1 and 2-years post-operative. All HRQOL measures were normalized to each patient's baseline scores. A 2-year IHS was calculated for each individual patient the means compared between groups. RESULTS: 149 patients were included (/=65:50). All groups significantly improved in all HRQOL at 2-years compared to baseline (p/=65:50). All groups significantly improved in all HRQOL at 2-years compared to baseline (p0.05). Normalized IHS HRQOL for young patients was worse than elderly for ODI, PCS, MCS, SRS activity, pain and total over the 2-year recovery period from index surgery. The MILD ODI group had significantly worse 2-year IHS values than the HIGH group for all HRQOL measured (p0.05). CONCLUSION: Contrary to our hypothesis, an integrated health state analysis suggested that the recovery process was significantly better for elderly patients than young patients and better for patients with high baseline disability.

Schenning, K. J., & Deiner, S. G. (2015). Postoperative delirium in the geriatric patient. *Anesthesiology Clinics,*

Postoperative delirium, a common complication in older surgical patients, is independently associated with increased morbidity and mortality. Patients older than 65years receive greater than one-third of the more than 40 million anesthetics delivered yearly in the United States. This number is expected to increase with the aging of the population. Thus, it is increasingly important that perioperative clinicians who care for geriatric patients have an understanding of the complex syndrome of postoperative delirium. © 2015 Elsevier Inc.

Schmidt, M. A., Kurosky, S. K., Mullooly, J. P., Chun, C., & Weinmann, S. (2015). A ten-year case-
control study of passive smoke exposure as a risk factor for pertussis in children. *The
Permanente Journal, 19*(3), 59-63.

The authors conducted a matched case-control study of laboratory-confirmed pertussis cases,
occurring from 1/1/1996 to 12/31/2005, in children up to 12 years of age who were members of
a large managed care organization. Sixty-five laboratoryconfirmed cases of pertussis were
identified. Using multivariable conditional logistic regression analysis, the authors did not detect a
statistically significant association between pertussis and household passive exposure to cigarette
smoking.

Schreiber, M. A. (2015). Determining outcomes after traumatic brain injury. *JAMA Surgery,*

Scoles, D., Flatter, J. A., Cooper, R. F., Langlo, C. S., Robison, S., Neitz, M., et al. (2015). Assessing
photoreceptor structure associated with ellipsoid zone disruptions visualized with optical
coherence tomography. *Retina (Philadelphia, Pa.),*

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.

Scott Polackwich, A., Tadros, N. N., Ostrowski, K. A., Kent, J., Conlin, M. J., Hedges, J. C., et al. (2015). Vasectomy reversal for postvasectomy pain syndrome: A study and literature review. *Urology,*

OBJECTIVE: To review our institution's experience and success with vasectomy reversal to treat postvasectomy pain syndrome (PVPS) over the last 20 years. MATERIALS AND METHODS: A single surgeon (E.F.F.) performed all the vasectomy reversals. We identified 123 procedures done for PVPS treatment and were able to contact 76 patients. We sent surveys or conducted phone interviews inquiring about satisfaction, levels of pain preoperatively and postoperatively, and the need for additional procedures for pain. Thirty-one patients completed phone or written surveys. In addition, we compared the location of vasectomy among patients presenting for pain to that of fertile patients. RESULTS: Thirty-one men had vasectomy reversal for postvasectomy pain, with median age of 38 years (range, 31-55 years), of which 26 underwent vasovasostomy (VV). Seven patients required epididymovasostomy (EV) on at least 1 side based on intraoperative findings. Eighty-two percent of patients reported improvement in their pain at 3.2 months (+/-3.4 months) after vasectomy reversal. Thirty-four percent patients had complete resolution of all pain. Mean pain score before procedure was 6.4 (+/-2.4), decreasing to a median of 2.7 (+/-2.7) afterward. There was a 59% improvement in pain scores (P <.001). Two patients required additional procedures for continued pain, one orchiectomy and one epididymectomy. Four patients required an additional reversal procedure, one a repeat VV at 1 year and 3 an EV at 1, 5, and 9 years, respectively. Follow-up ranged from 1 to 19 years, with a mean follow-up of 8.4 years. We found no relationship between vasectomy location and pain. CONCLUSION: Vasectomy reversal, through the use of both VV and EV, can provide long-term relief from PVPS.

Seelye, A., Mattek, N., Howieson, D. B., Austin, D., Wild, K., Dodge, H. H., et al. (2015). Embedded online questionnaire measures are sensitive to identifying mild cognitive impairment. *Alzheimer Disease and Associated Disorders,*

BACKGROUND/AIMS: Early changes in cognitively demanding daily activities occur between normal cognition and the development of mild cognitive impairment (MCI). These real-world functional changes as early signals of cognitive change form a prime target for meaningful early detection of dementia. We examined whether passive aspects of responding to a remotely

monitored weekly online questionnaire discriminated between older adults with and without MCI. METHODS: Participants were 83 independent, community-dwelling older adults enrolled in a longitudinal study of in-home monitoring technologies, which included completion of a short weekly online questionnaire of health and life events. RESULTS: In longitudinal analyses, time to complete the online questionnaire decreased over 1 year in both MCI and cognitively intact participants (P<0.01). MCI and intact participants did not differ in the time of day they submitted their questionnaires initially; however, over the course of 1 year MCI participants began to submit their questionnaires progressively later in the day and they needed greater assistance from staff as compared with intact participants (P<0.05). The online questionnaire performance measures were significantly correlated to conventional cognitive test scores (P<0.05) across the spectrum of normal cognition to MCI. CONCLUSIONS: Ambiently assessed, passive performance measures embedded within an online questionnaire are able to discriminate between normal cognition and MCI. Remote monitoring of cognitively demanding routine daily activities is a promising approach for ecologically valid real-world cognitive assessment.

Selph, S., Dana, T., Blazina, I., Bougatsos, C., Patel, H., & Chou, R. (2015). Screening for type 2 diabetes mellitus: A systematic review for the U.S. preventive services task force. *Annals of Internal Medicine, 162*(11), 765-776.

Background: Screening for type 2 diabetes mellitus could lead to earlier identification and treatment of asymptomatic diabetes, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), potentially resulting in improved outcomes. Purpose: To update the 2008 U.S. Preventive Services Task Force review on diabetes screening in adults. Data Sources: Cochrane databases and MEDLINE (2007 through October 2014) and relevant studies from previous Task Force reviews. Study Selection: Randomized, controlled trials; controlled, observational studies; and systematic reviews. Data Extraction: Data were abstracted by 1 investigator and checked by a second; 2 investigators independently assessed study quality. Data Synthesis: In 2 trials, screening for diabetes was associated with no 10-year mortality benefit versus no screening (hazard ratio, 1.06 [95% CI, 0.90 to 1.25]). Sixteen trials consistently found that treatment of IFG or IGT was associated with delayed progression to diabetes. Most trials of treatment of IFG or IGT found no effects on all-cause or cardiovascular mortality, although lifestyle modification was

associated with decreased risk for both outcomes after 23 years in 1 trial. For screen-detected

diabetes, 1 trial found no effect of an intensive multifactorial intervention on risk for all-cause or

cardiovascular mortality versus standard control. In diabetes that was not specifically

screendetected, 9 systematic reviews found that intensive glucose control did not reduce risk for

all-cause or cardiovascular mortality and results for intensive blood pressure control were

inconsistent.

Sengle, G., Carlberg, V., Tufa, S. F., Charbonneau, N. L., Smaldone, S., Carlson, E. J., et al. (2015).
Abnormal activation of BMP signaling causes myopathy in Fbn2 null mice. *PLoS Genetics, 11*(6),
e1005340.

Fibrillins are large extracellular macromolecules that polymerize to form the backbone structure

of connective tissue microfibrils. Mutations in the gene for fibrillin-1 cause the Marfan syndrome,

while mutations in the gene for fibrillin-2 cause Congenital Contractural Arachnodactyly. Both are

autosomal dominant disorders, and both disorders affect musculoskeletal tissues. Here we show

that Fbn2 null mice (on a 129/Sv background) are born with reduced muscle mass, abnormal

muscle histology, and signs of activated BMP signaling in skeletal muscle. A delay in Myosin

Heavy Chain 8, a perinatal myosin, was found in Fbn2 null forelimb muscle tissue, consistent with

the notion that muscle defects underlie forelimb contractures in these mice. In addition, white fat

accumulated in the forelimbs during the early postnatal period. Adult Fbn2 null mice are already

known to demonstrate persistent muscle weakness. Here we measured elevated creatine kinase

levels in adult Fbn2 null mice, indicating ongoing cycles of muscle injury. On a C57Bl/6

background, Fbn2 null mice showed severe defects in musculature, leading to neonatal death

from respiratory failure. These new findings demonstrate that loss of fibrillin-2 results in

phenotypes similar to those found in congenital muscular dystrophies and that FBN2 should be

considered as a candidate gene for recessive congenital muscular dystrophy. Both in vivo and in

vitro evidence associated muscle abnormalities and accumulation of white fat in Fbn2 null mice

with abnormally activated BMP signaling. Genetic rescue of reduced muscle mass and

accumulation of white fat in Fbn2 null mice was accomplished by deleting a single allele of Bmp7.

In contrast to other reports that activated BMP signaling leads to muscle hypertrophy, our

findings demonstrate the exquisite sensitivity of BMP signaling to the fibrillin-2 extracellular

environment during early postnatal muscle development. New evidence presented here suggests that fibrillin-2 can sequester BMP complexes in a latent state.

Shaw, B. E., Logan, B. R., Kiefer, D. M., Chitphakdithai, P., Pedersen, T. L., Abdel-Azim, H., et al. (2015). Analysis of the effect of race, socioeconomic status, and center size on unrelated national marrow donor program donor outcomes: Donor toxicities are more common at low-volume bone marrow collection centers. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation,*

Previous studies have shown that risks of collection-related pain and symptoms are associated with sex, body mass index, and age in unrelated donors undergoing collection at National Marrow Donor Program centers. We hypothesized that other important factors (race, socioeconomic status [SES], and number of procedures at the collection center) might affect symptoms in donors. We assessed outcomes in 2726 bone marrow (BM) and 6768 peripheral blood stem cell (PBSC) donors collected between 2004 and 2009. Pain/symptoms are reported as maximum levels over mobilization and collection (PBSC) or within 2 days of collection (BM) and at 1 week after collection. For PBSC donors, race and center volumes were not associated with differences in pain/symptoms at any time. PBSC donors with high SES levels reported higher maximum symptom levels 1 week after donation (P = .017). For BM donors, black males reported significantly higher levels of pain (OR, 1.90; CI, 1.14 to 3.19; P = .015). No differences were noted by SES group. BM donors from low-volume centers reported more toxicity (OR, 2.09; CI, 1.26 to 3.46; P = .006). In conclusion, race and SES have a minimal effect on donation-associated symptoms. However, donors from centers performing </= 1 BM collection every 2 months have more symptoms after BM donation. Approaches should be developed by registries and low-volume centers to address this issue.

Sheffet, A. J., Voeks, J. H., Mackey, A., Brooks, W., Clark, W. M., Hill, M. D., et al. (2015). Characteristics of participants consenting versus declining follow-up for up to 10 years in a randomized clinical trial. *Clinical Trials (London, England),*

BACKGROUND: With patients living a decade or longer post-procedure, long-term data are needed to assess the durability of carotid artery stenting versus carotid endarterectomy.

Identifying characteristics of those consenting or declining to continue in long-term follow-up may suggest strategies to improve retention in clinical trials. PURPOSE: This report describes differences between patients choosing or declining to continue follow-up for up to 10 years in the Carotid Revascularization Endarterectomy versus Stenting Trial. METHODS: Following completion of the primary outcome, patients who were in active Carotid Revascularization Endarterectomy versus Stenting Trial follow-up were asked to continue beyond their original 4-year commitment for a maximum of 10 years. The characteristics of those who consented were compared with those who declined. Univariate and multivariable logistic regression were used for analysis, and backwards stepwise logistic regression (the most parsimonious model) was used to determine the factors associated with continuation. RESULTS: Of the 1921 active Carotid Revascularization Endarterectomy versus Stenting Trial participants for whom consent to extend follow-up was requested, 1695 (88%; mean age: 68.4) consented; 226 (12%; mean age: 69.6) declined. Of those who did not consent versus those who consented, 66% versus 48% were symptomatic at baseline (p < 0.0001), at follow-up 28% versus 20% were smokers (p = 0.009), 85% versus 90% were hypertensive (p = 0.01), and 84% versus 94% were dyslipidemic (p < 0.0001). Additional factors that differed between those who did not consent and those who consented included the mean number of years in the study at time of consent (4.8 years vs 3.7 years (p = <0.0001)) and patients from sites that enrolled </=30 patients compared to sites randomizing 30 or more (70% vs 52% (p < 0.0001)). Multivariable logistic regression indicated that those with lesser odds of consenting to the extended follow-up were older (odds ratio: 0.80; 95% confidence interval: 0.67, 0.96), more likely to be symptomatic (odds ratio: 0.58; 95% confidence interval: 0.42, 0.80), smokers (odds ratio: 0.48; 95% confidence interval: 0.34, 0.70), were in the study 5+ years versus <3 (odds ratio: 0.21; 95% confidence interval: 0.13, 0.34), and at a site that randomized <30 patients (odds ratio: 0.46; 95% confidence interval: 0.33, 0.63), while patients with dyslipidemia at follow-up had increased odds of consenting (odds ratio: 2.28 (1.47, 3.54)). CONCLUSION: Symptomatic status, increasing age, randomized at lower volume centers, and longer time in follow-up were associated with reduced odds of consenting to long-term follow-up. Identifying factors associated with reduced willingness to extend participation long-term can suggest targeted strategies to improve retention in future clinical trials.

Shim, C. Y., Liu, Y. N., Atkinson, T., Xie, A., Foster, T., Davidson, B. P., et al. (2015). Molecular imaging of platelet-endothelial interactions and endothelial von willebrand factor in early and mid-stage atherosclerosis. *Circulation.Cardiovascular Imaging, 8*(7), 10.1161/CIRCIMAGING.114.002765.

BACKGROUND: Nonthrombotic platelet-endothelial interactions may contribute to atherosclerotic plaque development, although in vivo studies examining mechanism without platelet preactivation are lacking. Using in vivo molecular imaging at various stages of atherosclerosis, we quantified platelet-endothelial interactions and evaluated the contribution of major adhesion pathways. METHODS AND RESULTS: Mice deficient for the low-density lipoprotein receptor and Apobec-1 were studied as an age-dependent model of atherosclerosis at 10, 20, 30, and 40 weeks of age, which provided progressive increase in stage from early fatty streak (10 weeks) to large complex plaques without rupture (40 weeks). Platelet-targeted contrast ultrasound molecular imaging of the thoracic aorta performed with microbubbles targeted to GPIbalpha demonstrated selective signal enhancement as early as 10 weeks of age. This signal increased progressively with age (almost 8-fold increase from 10 to 40 weeks, analysis of variance P<0.001). Specificity for platelet targeting was confirmed by the reduction in platelet-targeted signal commensurate with the decrease in platelet count after immunodepletion with anti-GPIb or anti-CD41 antibody. Inhibition of P-selectin in 20 and 40 weeks atherosclerotic mice resulted in a small (15% to 30%) reduction in platelet signal. Molecular imaging with microbubbles targeted to the A1 domain of von Willebrand factor demonstrated selective signal enhancement at all time points, which did not significantly increase with age. Treatment of 20 and 40 week mice with recombinant ADAMTS13 eliminated platelet and von Willebrand factor molecular imaging signal. CONCLUSIONS: Platelet-endothelial interactions occur in early atherosclerosis. These interactions are in part caused by endothelial von Willebrand factor large multimers, which can be reversed with exogenous ADAMTS13.

Shnayder, Y., Lin, D., Desai, S. C., Nussenbaum, B., Sand, J. P., & Wax, M. K. (2015). Reconstruction of the lateral mandibular defect: A review and treatment algorithm. *JAMA Facial Plastic Surgery,* Reconstruction of the lateral mandibular defect presents a complex challenge to the reconstructive surgeon, often involving interconnected soft-tissue and bone requirements. This

review examines the current literature on functional outcomes of lateral mandibular reconstruction and presents an algorithm on selecting an optimal reconstructive choice for patients with lateral mandibular defects resulting from oncologic ablative surgery or trauma. PubMed and Medline searches on reconstructing lateral mandibular defect were performed of the English literature. Search terms included lateral mandibular defect, outcomes of mandibular reconstruction, and free flap reconstruction of mandible. Although most of the articles presented are retrospective reviews, priority was given to the articles with high-quality level of evidence. Restoration of function, including speech and swallow, and acceptable cosmetic result are the primary objectives of lateral mandibular reconstruction. When reconstructing the mandible in a patient following tumor extirpation, the patient's overall prognosis, medical comorbidities, and need for adjuvant therapy should be considered. In the patient with aggressive malignant disease and a poor prognosis, a less complex reconstruction, such as soft-tissue flap with or without a reconstruction plate, may be adequate. In a dentate patient with favorable prognosis, a durable reconstruction, such as osseocutaneous microvascular free flap, is often preferred. Various reconstructive options are available for patients with lateral mandibular defects. Depending on the predominance of the soft-tissue or bony components of the defect, with consideration of the patient's characteristics and functional and aesthetic goals, the surgeon can wisely select from these reconstructive possibilities.

Silverberg, J. I., Patel, N., Immaneni, S., Rusniak, B., Silverberg, N. B., Debashis, R., et al. (2015). Assessment of atopic dermatitis using self- and caregiver- report: A multicenter validation study. *The British Journal of Dermatology,*
BACKGROUND: The epidemiology of atopic dermatitis (AD) in the US has largely been described via US population-based questionnaire studies. However, the validity of the questions used for self- and caregiver-reported eczema has not been previously demonstrated. METHODS: We performed a prospective multicenter dermatology practice-based study (3 sites) to determine the validity of caregiver- and self-reported ever and 1-year history of eczema. Questionnaires were administered to unselected patients prior to their encounter. Patients (n=782) were then evaluated by expert dermatologists trained in utilizing the Hanifin and Rajka criteria for AD. Sensitivity, specificity, positive and negative predictive value were determined. RESULTS:

Caregiver reported 1-year history of childhood eczema was found to have a sensitivity of 0.70 (95% confidence interval: 0.59-0.80), specificity of 0.96 (0.93-0.99) and PPV of 0.87 (0.78-0.96) when compared to a physician diagnosis of AD at that visit. Similarly, self-reported 1-year history of adult eczema was found to have a sensitivity of 0.70 (0.59-0.80), specificity of 0.95 (0.93-0.97) and positive predictive value of 0.76 (0.64-0.85). The specificity and PPV of ever-history of caregiver- (0.89 [0.82-0.96] and 0.81 [0.70-0.93]) and self-reported eczema (0.97 [0.95-0.99] and 0.91 [0.85-0.97]) were high, with a high sensitivity in children (0.83 [0.72 0.95]) but not adults (0.43 [0.37-0.51]). CONCLUSIONS: Self- and caregiver-reported diagnosis of eczema ever or in the past year based on a single question demonstrates sufficient validity for the epidemiological study of AD. This article is protected by copyright. All rights reserved.

Simpson, D., Meredith, J., Boyer, K., Dilts, D., Ellram, L. M., & Leong, G. K. (2015). Professional, research, and publishing trends in operations and supply chain management. *Journal of Supply Chain Management, 51*(3), 87-100.

We report on the thoughts of a large group of scholars in the field of operations and supply chain management (O/SCM) regarding current and future issues facing our profession. Broad issues raised and addressed include a perceived lack of relevance in our research, calls from business school deans for faculty to increasingly fund their own research, greater demand for use of large data sets and methodological rigor, along with higher expectations for publishing. We invited four scholars who discussed these issues during an Academy of Management conference session in 2014, to present their perspectives within this essay. We then distributed the perspectives of each of these authors to O/SCM scholars globally so that they could add support, counterpoints, and extensions. Collectively, they raise important points regarding a need for greater innovation and creativity in O/SCM research, the challenges and opportunities of increased complexity and "big data," the value of working in other research domains and collaborating with others, the promise of new technology, and the importance of improving how we communicate our value to business school colleagues. Finally, our contributors provide recommendations on how we may address these issues and continue to adapt and move our profession forward. © 2015 Institute for Supply Management, Inc.

Smith, M. L., Li, J., & Ryabinin, A. E. (2015). Increased alcohol consumption in urocortin 3 knockout

mice is unaffected by chronic inflammatory pain. *Alcohol and Alcoholism, 50*(2), 132-139.

Aims: Stress neurocircuitry may modulate the relationship between alcohol drinking and chronic

pain. The corticotropin-releasing factor (CRF) system is crucial for regulation of stress responses.

The current study aimed to elucidate the role of the endogenous CRF ligand Urocortin 3 (Ucn3) in

the relationship between alcohol drinking behavior and chronic pain using a genetic approach.

Methods: Ucn3 (KO) and wildtype (WT) littermates were subjected to a 24-h access drinking

procedure prior to and following induction of chronic inflammatory pain. Results: Ucn3 KO mice

displayed significantly increased ethanol intake and preference compared with WT across the

time course. There were no long-term effects of chronic pain on alcohol drinking behavior,

regardless of genotype, nor any evidence for alcohol-induced analgesia. Conclusion: The

increased drinking in Ucn3 KO supports a role for this peptide in alcohol-related behavior. These

data suggest the necessity for more research exploring the relationship between alcohol drinking,

chronic pain and the CRF system in rodent models. © The Author 2014. Medical Council on

Alcohol and Oxford University Press. All rights reserved.

Soni, C., Domeier, P. P., Wong, E. B., Shwetank, Khan, T. N., Elias, M. J., et al. (2015). Distinct and

synergistic roles of FcγRIIB deficiency and 129 strain-derived SLAM family proteins in the

development of spontaneous germinal centers and autoimmunity. *Journal of Autoimmunity,*

The inhibitory IgG Fc receptor (FcγRIIB) deficiency and 129 strain-derived signaling lymphocyte

activation molecules (129-SLAMs) are proposed to contribute to the lupus phenotype in FcγRIIB-

deficient mice generated using 129ES cells and backcrossed to C57BL/6 mice (B6.129.RIIBKO).

In this study, we examine the individual contributions and the cellular mechanisms by which

FcγRIIB deficiency and 129-derived SLAM family genes promote dysregulated spontaneous

germinal center (Spt-GC) B cell and follicular helper T cell (Tfh) responses in B6.129.RIIBKO

mice. We find that B6 mice congenic for the 129-derived SLAM locus (B6.129-SLAM) and B6 mice

deficient in FcγRIIB (B6.RIIBKO) have increased Spt-GC B cell responses compared to B6 controls

but significantly lower than B6.129.RIIBKO mice. These data indicate that both FcγRIIB deficiency

and 129-SLAMs contribute to elevated Spt-GC B cell responses in B6.129.RIIBKO mice. However,

only 129-SLAMs contribute significantly to augmented Tfh responses in B6.129.RIIBKO mice, and

do so by a combination of T cell-dependent effects and enhanced B cell and DC-dependent antigen presentation to T cells. Elevated Spt-GC B cell responses in mice with FcγRIIB deficiency and polymorphic 129-SLAMs were associated with elevated metabolic activity, improved GC B cell survival and increased differentiation of naïve B cells into GC B cell phenotype. Our data suggest that the interplay between 129-SLAM expression on B cells, T cells and DCs is central to the alteration of the GC tolerance checkpoint, and that deficiency of FcγRIIB on B cells is necessary to augment Spt-GC responses, pathogenic autoantibodies, and lupus disease. © 2015 Elsevier Ltd.

Soto, P. L., Hiranita, T., Xu, M., Hursh, S. R., Grandy, D. K., & Katz, J. L. (2015). Dopamine D-like receptors and behavioral economics of food reinforcement. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology,*

Previous studies suggest dopamine (DA) D2-like receptor involvement in the reinforcing effects of food. To determine contributions of the three D2-like receptor subtypes, knockout (KO) mice completely lacking DA receptors (D2R, D3R, or D4R KO mice) and their wild-type littermates were exposed to a series of fixed-ratio (FR) food-reinforcement schedules in two contexts: an open economy with additional food provided outside the experimental setting and a closed economy with all food earned within the experimental setting. A behavioral-economic model was used to quantify reinforcer effectiveness with food pellets obtained as a function of price (FR schedule value) plotted to assess elasticity of demand. Under both economies, as price increased, food pellets obtained decreased more rapidly (i.e., food demand was more elastic) in DA D2R KO mice compared to WT littermates. Extinction of responding was studied in two contexts: by eliminating food deliveries and by delivering food independently of responding. A hyperbolic model quantified rates of extinction. Extinction in DA D2R KO mice occurred less rapidly compared to WT mice in both contexts. Elasticity of food demand was higher in DA D4R KO than WT mice in the open, but not closed, economy. Extinction of responding in DA D4R KO mice was not different from that in WT littermates in either context. No differences in elasticity of food demand or extinction rate were obtained in D3R KO mice and WT littermates. These results indicate that the D2R is the primary DA D2-like receptor subtype mediating the reinforcing

effectiveness of food.Neuropsychopharmacology accepted article preview online, 24 July 2015. doi:10.1038/npp.2015.223.

Sparks, T. N., Yeaton-Massey, A., Granados, J. M., Handler, S. J., Meyer, M., & Caughey, A. B. (2015). How do maternal views of delivery outcomes vary by demographics and preferred mode of delivery? *American Journal of Perinatology, 32*(8), 741-746.

Objective To investigate how maternal views of delivery outcomes vary by demographic characteristics and preference toward mode of delivery (MOD). Study Design Survey of 719 pregnant women in outpatient clinics at an academic institution during their third trimester. Women ranked outcomes such as vaginal delivery (VD), cesarean delivery (CD), urinary incontinence, perineal lacerations, and induction of labor (IOL) on a visual analog scale (VAS) in order of worst imaginable (0) to best possible (100) outcomes. Results Women of all ages ranked VD as more desirable than CD. However, women ≥ 35 years of age had greater valuations of both MOD compared with women <35 years, with mean VAS scores of 88.4 versus 86.4 for VD (p<0.001) and 61.5 versus 51.9 for CD (p<0.001). Women with a college education or higher also rated both MOD as more desirable than women with less than a college education. Additionally, women who preferred VD rather than CD had greater valuations of perineal laceration (43.3 vs. 31.5, p=0.001) and urinary incontinence (40.7 vs. 30.1, p=0.002). Conclusion Significant differences exist in women's views toward MOD and peripartum outcomes, by demographics and preferred MOD. Understanding delivery preferences better enables clinicians to counsel women about labor and management options. © 2015 by Thieme Medical Publishers, Inc.

Starr, J., Castro, E., Crosas, M., Dumontier, M., Downs, R. R., Duerr, R., et al. (2015). Achieving human and machine accessibility of cited data in scholarly publications. *PeerJ.Computer Science, 1*, e1.

Reproducibility and reusability of research results is an important concern in scientific communication and science policy. A foundational element of reproducibility and reusability is the open and persistently available presentation of research data. However, many common approaches for primary data publication in use today do not achieve sufficient long-term

robustness, openness, accessibility or uniformity. Nor do they permit comprehensive exploitation by modern Web technologies. This has led to several authoritative studies recommending uniform direct citation of data archived in persistent repositories. Data are to be considered as first-class scholarly objects, and treated similarly in many ways to cited and archived scientific and scholarly literature. Here we briefly review the most current and widely agreed set of principle-based recommendations for scholarly data citation, the Joint Declaration of Data Citation Principles (JDDCP). We then present a framework for operationalizing the JDDCP; and a set of initial recommendations on identifier schemes, identifier resolution behavior, required metadata elements, and best practices for realizing programmatic machine actionability of cited data. The main target audience for the common implementation guidelines in this article consists of publishers, scholarly organizations, and persistent data repositories, including technical staff members in these organizations. But ordinary researchers can also benefit from these recommendations. The guidance provided here is intended to help achieve widespread, uniform human and machine accessibility of deposited data, in support of significantly improved verification, validation, reproducibility and re-use of scholarly/scientific data.

Stephenson, E. J. P., & Liem, T. K. (2015). Duplex imaging of residual venous obstruction to guide duration of therapy for lower extremity deep venous thrombosis. *Journal of Vascular Surgery: Venous and Lymphatic Disorders, 3*(3), 326-332.

Background Clinical trials have shown that the presence of ultrasound-identified residual venous obstruction (RVO) on follow-up scanning may be associated with an elevated risk for recurrence, thus providing a potential tool to help determine the optimal duration of anticoagulant therapy. We performed a systematic review to evaluate the clinical utility of post-treatment duplex imaging in predicting venous thromboembolism (VTE) recurrence and in adjusting duration of anticoagulation. Methods The Ovid MEDLINE Database, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects were queried for the terms residual thrombus or obstruction, duration of therapy, deep vein thrombosis, deep venous thrombosis, DVT, venous thromboembolism, VTE, antithrombotic therapy, and anticoagulation, and 228 studies were selected for review. Six studies determined the rate of VTE recurrence on the basis of the presence or absence of RVO. Results Findings on

venous ultrasound scans frequently remained abnormal in 38% to 80% of patients, despite at least 3 months of therapeutic anticoagulation. In evaluating for VTE recurrence, the definition of RVO varied widely in the literature. Some studies have shown an association between RVO and VTE recurrence, whereas other studies have not. Overall, the presence of RVO is a mild risk factor for recurrence (odds ratio, 1.3-2.0), but only when surveillance imaging is performed soon after the index deep venous thrombosis (3 months). Conclusions RVO is a mild risk factor for VTE recurrence. The presence or absence of ultrasound-identified RVO has a limited role in guiding the duration of therapeutic anticoagulation. Further research is needed to evaluate its utility relative to other known risk factors for VTE recurrence. © 2015 Society for Vascular Surgery.

Stock, R., Hall, J., Chang, A. M., & Cohen, D. (2015). Physicians' early perspectives on oregon's coordinated care organizations. *Healthcare,*

Background: Through development of Coordinated Care Organizations (CCOs), Oregon's version of the Accountable Care Organization (ACO) for Medicaid beneficiaries, Oregon is redesigning the healthcare system delivering care to some of its most vulnerable citizens. While clinicians are central to healthcare transformation, little is known about the impact on their role. The aim of this study was to understand the current and perceived effect CCO-related changes have on Oregon physicians' professional and personal lives. Methods: This qualitative observational study involved semi-structured interviews, conducted between March and October, 2013, of twenty-two purposively selected physicians who varied in years of practice, gender, employment status, specialty, and geographic location from three different CCOs. A grounded theory approach was used to analyze data. Results: Physicians expressed uncertainty and ambiguity about the CCO model, reporting minor financial changes in the first year, but anticipating future reimbursement changes; new team-based care roles and responsibilities, accountability for quality incentive measures; and effects of CCO implementation on their personal lives. To meet CCO model changes and requirements, physicians requested collegial networking, team-based care training, and data system and information technology support for undergoing health system transformation. Conclusions: Although perhaps not immediate, healthcare reform can have a real and perceived impact on physicians' professional and personal lives. Implications: Attention to the impact of healthcare reform on physicians' personal and professional lives is important to

ensure strategies are implemented to maintain a viable workforce, professional satisfaction, financial sustainability, and quality of care. © 2015 Elsevier Inc.

Sun, B. C., Laurie, A., Prewitt, L., Fu, R., Chang, A. M., Augustine, J., et al. (2015). Risk-adjusted variation of publicly reported emergency department timeliness measures. *Annals of Emergency Medicine,*
STUDY OBJECTIVE: The Centers for Medicare & Medicaid Services (CMS) recently published emergency department (ED) timeliness measures. These data show substantial variation in hospital performance and suggest the need for process improvement initiatives. However, the CMS measures are not risk adjusted and may provide misleading information about hospital performance and variation. We hypothesize that substantial hospital-level variation will persist after risk adjustment. METHODS: This cross-sectional study included hospitals that participated in the Emergency Department Benchmarking Alliance and CMS ED measure reporting in 2012. Outcomes included the CMS measures corresponding to median annual boarding time, length of stay of admitted patients, length of stay of discharged patients, and waiting time of discharged patients. Covariates included hospital structural characteristics and case-mix information from the American Hospital Association Survey, CMS cost reports, and the Emergency Department Benchmarking Alliance. We used a gamma regression with a log link to model the skewed outcomes. We used indirect standardization to create risk-adjusted measures. We defined "substantial" variation as coefficient of variation greater than 0.15. RESULTS: The study cohort included 723 hospitals. Risk-adjusted performance on the CMS measures varied substantially across hospitals, with coefficient of variation greater than 0.15 for all measures. Ratios between the 10th and 90th percentiles of performance ranged from 1.5-fold for length of stay of discharged patients to 3-fold for waiting time of discharged patients. CONCLUSION: Policy-relevant variations in publicly reported CMS ED timeliness measures persist after risk adjustment for nonmodifiable hospital and case-mix characteristics. Future "positive deviance" studies should identify modifiable process measures associated with high performance.

Taber, J. M., Aspinwall, L. G., Stump, T. K., Kohlmann, W., Champine, M., & Leachman, S. A. (2015). Genetic test reporting enhances understanding of risk information and acceptance of prevention

recommendations compared to family history-based counseling alone. *Journal of Behavioral*

Medicine,

It is unknown whether or why genetic test reporting confers benefits in the understanding and

management of cancer risk beyond what patients learn from counseling based on family history.

A prospective nonexperimental control group study compared participants from melanoma-prone

families who underwent CDKN2A/p16 (p16) genetic testing (27 carriers, 38 noncarriers) to

participants from equivalently melanoma-prone families known not to carry a deleterious p16

mutation (31 no-test controls). All participants received equivalent counseling concerning

elevated lifetime melanoma risk and corresponding recommendations for prevention and

screening. Both immediately and 1 month after counseling, participants receiving a genetic test

result reported greater understanding of their risk, decreased derogation of the risk information,

and greater personal applicability of prevention recommendations than no-test controls.

Decreased derogation of risk information after test reporting predicted further increases in

understanding of melanoma risk and applicability of prevention recommendations 1 month later.

Results suggest unique benefits of genetic test reporting in promoting understanding and

acceptance of information about hereditary cancer risk and its management. © 2015 Springer

Science+Business Media New York

Tan, O., Liu, G., Liang, L., Gao, S. S., Pechauer, A. D., Jia, Y., et al. (2015). En face doppler total

retinal blood flow measurement with 70 kHz spectral optical coherence tomography. *Journal of*

Biomedical Optics, 20(6)

An automated algorithm was developed for total retinal blood flow (TRBF) using 70-kHz spectral

optical coherence tomography (OCT). The OCT was calibrated for the transformation from

Doppler shift to speed based on a flow phantom. The TRBF scan pattern contained five repeated

volume scans (2 × 2 mm) obtained in 3 s and centered on central retinal vessels in the optic

disc. The TRBF was calculated using an en face Doppler technique. For each retinal vein, blood

flow was measured at an optimal plane where the calculated flow was maximized. The TRBF was

calculated by summing flow in all veins. The algorithm tracked vascular branching so that either

root or branch veins are summed, but never both. The TRBF in five repeated volumes were

averaged to reduce variation due to cardiac cycle pulsation. Finally, the TRBF was corrected for

eye length variation. Twelve healthy eyes and 12 glaucomatous eyes were enrolled to test the algorithm. The TRBF was 45.4 ± 6.7 µl/min for healthy control and 34.7 ± 7.6 µl/min for glaucomatous participants (p-value = 0.01). The intravisit repeatability was 8.6% for healthy controls and 8.4% for glaucoma participants. The proposed automated method provided repeatable TRBF measurement. © 2015 Society of Photo-Optical Instrumentation Engineers.

Tarasidis, G. S., Deconde, A. S., Mace, J. C., Ashby, S., Smith, T. L., Orlandi, R. R., et al. (2015). Cognitive dysfunction associated with pain and quality of life in chronic rhinosinusitis. *International Forum of Allergy and Rhinology,*
Background: Cognitive dysfunction and its relationship to both pain and disease-specific quality of life (QOL) in chronic rhinosinusitis (CRS) have not been investigated previously. We sought to analyze the correlations of pain and disease-specific QOL with cognitive function in CRS. Methods: Adults with CRS were prospectively enrolled in a cross-sectional study. Participants' cognitive function was assessed using the Cognitive Failures Questionnaire. Pain was characterized using the Short-Form McGill Pain Questionnaire (SF-MPQ) and the Brief Pain Inventory Short Form. Disease-specific QOL was ascertained using the Rhinosinusitis Disability Index (RSDI) and 22-item Sinonasal Outcome Test (SNOT-22). Disease severity was assessed using nasal endoscopy and computed tomography. Bivariate correlations of pain and cognitive dysfunction, disease-specific QOL, and clinical measures of disease severity were ascertained. Results: In patients with CRS (n = 70) there was a significant correlation between cognitive dysfunction and pain severity scores (Spearman's correlation [Rs] = 0.321, p] = 0.321, p s = 0.317, p = 0.317, p s = 0.498, p = 0.498, p s = 0.395, p = 0.395, p s = 0.528, p < 0.01). Conclusion: In patients with CRS, increasing pain and worse QOL are associated with cognitive dysfunction. Possible mechanisms for this cognitive dysfunction include differential neural activation secondary to chronic pain and/or the sequela of a chronic inflammatory state. © 2015 ARS-AAOA, LLC.

Tateno, M., Teo, A. R., & Tateno, Y. (2015). Eleven year follow-up of a boy with asperger syndrome and comorbid gender identity disorder of childhood. *Psychiatry and Clinical Neurosciences,*

Taylor, D. R., Venable, G. T., Jones, G. M., Lepard, J. R., Roberts, M. L., Saleh, N., et al. (2015). Five-year institutional bibliometric profiles for 103 US neurosurgical residency programs. *Journal of Neurosurgery,* , 1-14.

OBJECT Various bibliometric indices based on the citations accumulated by scholarly articles, including the h-index, g-index, e-index, and Google's i10-index, may be used to evaluate academic productivity in neurological surgery. The present article provides a comprehensive assessment of recent academic publishing output from 103 US neurosurgical residency programs and investigates intradepartmental publishing equality among faculty members. METHODS Each institution was considered a single entity, with the 5-year academic yield of every neurosurgical faculty member compiled to compute the following indices: ih(5), cumulative h, ig(5), ie(5), and i10(5) (based on publications and citations from 2009 through 2013). Intradepartmental comparison of productivity among faculty members yielded Gini coefficients for publications and citations. National and regional comparisons, institutional rankings, and intradepartmental publishing equality measures are presented. RESULTS The median numbers of departmental faculty, total publications and citations, ih(5), summed h, ig(5), ie(5), i10(5), and Gini coefficients for publications and citations were 13, 82, 716, 12, 144, 23, 16, 17, 0.57, and 0.71, respectively. The top 5 most academically productive neurosurgical programs based on ih(5)-index were University of California, San Francisco, University of California, Los Angeles, University of Pittsburgh, Brigham & Women's Hospital, and Johns Hopkins University. The Western US region was most academically productive and displayed greater intradepartmental publishing equality (median ih[5]-index = 18, median Ginipub = 0.56). In all regions, large departments with relative intradepartmental publishing equality tend to be the most academically productive. Multivariable logistic regression analysis identified the ih(5)-index as the only independent predictor of intradepartmental publishing equality (Ginipub $\leq$ 0.5 [OR 1.20, 95% CI 1.20-1.40, p = 0.03]). CONCLUSIONS The ih(5)-index is a novel, simple, and intuitive metric capable of accurately comparing the recent scholarly efforts of neurosurgical programs and accurately predicting intradepartmental publication equality. The ih(5)-index is relatively insensitive to factors such as isolated highly productive and/or no longer academically active senior faculty, which tend to distort other bibliometric indices and mask the accurate identification of currently productive academic environments. Institutional ranking by ih(5)-index

may provide information of use to faculty and trainee applicants, research funding institutions, program leaders, and other stakeholders.

Tedford, C. E., Delapp, S., Jacques, S., & Anders, J. (2015). Erratum: "quantitative analysis of transcranial and intraparenchymal light penetration in human cadaver brain tissue" (lasers in surgery and medicine (2015) 47(4):312-322). *Lasers in Surgery and Medicine, 47*(5), 466.

Terker, A. S., & Ellison, D. H. (2015). The renal mineralocorticoid receptor and electrolyte homeostasis. *American Journal of Physiology.Regulatory, Integrative and Comparative Physiology,* , ajpregu.00135.2015.
The renal mineralocorticoid receptor (MR) is a steroid hormone receptor essential for maintaining electrolyte homeostasis. Its role in mediating effects of aldosterone was likely vital in enabling the evolution of terrestrial life. Dysregulated aldosterone-MR signaling has been identified as the cause of multiple clinical diseases, suggesting the physiological importance of the MR. While the physiology of this pathway has been studied for over 60 years, only more recently have genetic mouse models been available to dissect its function in vivo. This review will focus on recent advances in our knowledge of MR function with an emphasis on these models.

Thiebes, K. P., Nam, H., Cambronne, X. A., Shen, R., Glasgow, S. M., Cho, H. H., et al. (2015). miR-218 is essential to establish motor neuron fate as a downstream effector of Isl1-Lhx3. *Nature Communications, 6*, 7718.
While microRNAs have emerged as an important component of gene regulatory networks, it remains unclear how microRNAs collaborate with transcription factors in the gene networks that determines neuronal cell fate. Here we show that in the developing spinal cord, the expression of miR-218 is directly upregulated by the Isl1-Lhx3 complex, which drives motor neuron fate. Inhibition of miR-218 suppresses the generation of motor neurons in both chick neural tube and mouse embryonic stem cells, suggesting that miR-218 plays a crucial role in motor neuron differentiation. Results from unbiased RISC-trap screens, in vivo reporter assays and overexpression studies indicated that miR-218 directly represses transcripts that promote developmental programs for interneurons. In addition, we found that miR-218 activity is required for Isl1-Lhx3 to effectively induce motor neurons and suppress interneuron fates. Together our

results reveal an essential role of miR-218 as a downstream effector of the Isl1-Lhx3 complex in establishing motor neuron identity.

Thomas, A. S., Baynham, J. T., & Flaxel, C. J. (2015). Macular holes, vitelliform lesions, and midperipheral retinoschisis in alport syndrome. *Retinal Cases & Brief Reports,*

PURPOSE: To describe the retinal findings in two cases of Alport syndrome. METHODS: Observational case series. The clinical findings of the two patients were documented with color fundus photography and high resolution spectral domain optical coherence tomography. RESULTS: Patient 1 was found to have fleck retinopathy in both eyes, inner retinal thinning in the right eye and a full-thickness macular hole in the left eye. Patient 2 was found to have a full-thickness macular hole in the right eye as well as retinoschisis in the temporal macula in the right eye. The left eye revealed inner retinal thinning involving the fovea, a vitelliform lesion of the temporal macula and midperipheral retinoschisis involving multiple retinal layers. CONCLUSION: Retinal abnormalities including fleck retinopathy, retinal thinning, macular holes, retinoschisis, and vitelliform lesions are variably present in Alport syndrome. This is only the second report of a vitelliform lesion in a patient with Alport syndrome and the first report of midperipheral retinoschisis. The array of retinal findings is believed to reflect a dysfunctional Type IV collagen present in the internal limiting membrane and Bruch membrane.

Thornburg, K. L. (2015). The programming of cardiovascular disease. *Journal of Developmental Origins of Health and Disease,* , 1-11.

In spite of improving life expectancy over the course of the previous century, the health of the U.S. population is now worsening. Recent increasing rates of type 2 diabetes, obesity and uncontrolled high blood pressure predict a growing incidence of cardiovascular disease and shortened average lifespan. The daily >$1billion current price tag for cardiovascular disease in the United States is expected to double within the next decade or two. Other countries are seeing similar trends. Current popular explanations for these trends are inadequate. Rather, increasingly poor diets in young people and in women during pregnancy are a likely cause of declining health in the U.S. population through a process known as programming. The fetal cardiovascular system is sensitive to poor maternal nutritional conditions during the periconceptional period, in the

womb and in early postnatal life. Developmental plasticity accommodates changes in organ

systems that lead to endothelial dysfunction, small coronary arteries, stiffer vascular tree, fewer

nephrons, fewer cardiomyocytes, coagulopathies and atherogenic blood lipid profiles in fetuses

born at the extremes of birthweight. Of equal importance are epigenetic modifications to genes

driving important growth regulatory processes. Changes in microRNA, DNA methylation patterns

and histone structure have all been implicated in the cardiovascular disease vulnerabilities that

cross-generations. Recent experiments offer hope that detrimental epigenetic changes can be

prevented or reversed. The large number of studies that provide the foundational concepts for

the developmental origins of disease can be traced to the brilliant discoveries of David J.P.

Barker.

Ting, A. Y., & Petroff, B. K. (2015). Challenges and potential for ovarian preservation with SERMs.
Biology of Reproduction, 92(5)

Tamoxifen (TAM) is a selective estrogen receptor modulator with tissue-specific effects on

estrogen signaling used predominantly for treatment and chemoprevention of breast cancers.

Recent studies have shown that TAM prevents infertility and decreases follicular loss from

common cancer chemotherapy and radiation therapy in preclinical models. Here we review

current and novel uses of selective estrogen receptor modulator s and advantages and challenges

for translation of TAM for human fertility preservation. © 2015 by the Society for the Study of

Reproduction, Inc.

Tipps, M. E., & Buck, K. J. (2015). *GIRK channels: A potential link between learning and addiction*
Academic Press Inc.

The ability of drug-associated cues to reinitiate drug craving and seeking, even after long periods

of abstinence, has led to the hypothesis that addiction represents a form of pathological learning,

in which drugs of abuse hijack normal learning and memory processes to support long-term

addictive behaviors. In this chapter, we review evidence suggesting that G protein-gated inwardly

rectifying potassium (GIRK/Kir3) channels are one mechanism through which numerous drugs of

abuse can modulate learning and memory processes. We will examine the role of GIRK channels

in two forms of experience-dependent long-term changes in neuronal function: homeostatic

plasticity and synaptic plasticity. We will also discuss how drug-induced changes in GIRK-mediated signaling can lead to changes that support the development and maintenance of addiction. © 2015 Elsevier Inc.

Tongtoyai, J., Todd, C. S., Chonwattana, W., Pattanasin, S., Chaikummao, S., Varangrat, A., et al. (2015). Prevalence and correlates of chlamydia trachomatis and neisseria gonorrhoeae by anatomic site among urban thai men who have sex with men. *Sexually Transmitted Diseases, 42*(8), 440-449.

BACKGROUND: Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) infection are prevalent among men who have sex with men (MSM) and may infect multiple anatomic sites. We measured site-specific prevalence and correlates of CT and NG infection among Bangkok MSM Cohort Study participants. METHODS: In April 2006 to November 2010, 1744 men enrolled in the Bangkok MSM Cohort Study. Participants provided historical information and underwent physical examination. Rectal, urethral, and pharyngeal CT and NG screening were performed by nucleic acid amplification and/or culture. Logistic regression was used to identify correlates of site-specific CT, NG, and coinfection. RESULTS: Among 1743 participants, 19.2% were infected with CT and/or NG. CT, NG, and CT-NG coinfection were detected in 11.6%, 4.6%, and 2.9%, of participants, respectively. Rectal, urethral, and pharyngeal CT infections were detected in 9.5%, 4.5%, and 3.6% of cases. N. gonorrhoeae was present at these sites in 6.1%, 1.8%, and 0.5% of cases. Most infections were asymptomatic (CT: 95.3%, NG: 83.2%). Rectal CT and NG infections were mutually associated (CT: adjusted odds ratio [AOR], 5.4; 95% confidence interval [CI], 3.4-8.7; NG: AOR, 2.4; 95% CI, 1.1-5.2) and independently associated with HIV infection (CT: AOR, 1.6, 95% CI, 1.0-2.4; NG: AOR, 2.0, 95% CI, 1.3-3.1). Numerous behavioral correlates of infection were observed. CONCLUSIONS: CT and NG infections are highly prevalent among MSM in Bangkok, most frequently affect the rectum, and are most often asymptomatic. Routine screening of asymptomatic MSM for CT and NG infection should include rectal sampling and focus on men with HIV and a history of other sexually transmitted infections.

Tsai, A. C., & Liu, X. (2014). Toward best practice in using molecular diagnosis to guide medical management, are we there yet? *North American Journal of Medicine & Science, 7*(4), 199-200.

Molecular genetics testing has made several huge breakthroughs in the past two decades and many molecular technologies have been applied to our daily medical progress. However, the clinical utility has not reach a consensus by the medical and genetic peers as well as third party payers. The predictive value and clinical applications are variable from one condition to the other. Numerous questions remain including technology deficits, data interpretation and unpredicted phenotypes in complex disorders. In this commentary, the authors reviewed the historical perspective of genetic testing and summarized the current technical deficit, clinical dilemma and suggested a few critical threshold to overcome before the implementation of useful genetic information in standard health care can become a reality.

Tullis, B. E., Ryals, R. C., Coyner, A. S., Gale, M. J., Nicholson, A., Ku, C., et al. (2015). Sarpogrelate, a 5-HT2A receptor antagonist, protects the retina from light-induced retinopathy. *Investigative Ophthalmology & Visual Science, 56*(8), 4560-4569.

PURPOSE: To determine if sarpogrelate, a selective 5-HT2A receptor antagonist, is protective against light-induced retinopathy in BALB/c mice. METHODS: BALB/c mice were dosed intraperitoneally with 5, 15, 30, 40, or 50 mg/kg sarpogrelate 48, 24, and 0 hours prior to bright light exposure (10,000 lux) as well as 24 and 48 hours after exposure. Additionally, a single injection regimen was evaluated by injecting mice with 50 mg/kg sarpogrelate once immediately prior to light exposure. To investigate the potential for additive effects of serotonin receptor agents, a combination therapy consisting of sarpogrelate (15 mg/kg) and 8-OH-DPAT (1 mg/kg) was evaluated with the 5-day treatment regimen. Neuroprotection was characterized by the preservation of retinal thickness and function, measured by spectral-domain optical coherence tomography (SD-OCT) and electroretinography (ERG), respectively. RESULTS: Mice that were light damaged and injected with saline had significantly reduced outer retinal thickness, total retinal thickness, and ERG amplitudes compared with naive mice. A 5-day administration of 15, 30, or 40 mg/kg of sarpogrelate was able to partially protect retinal morphology and full protection of retinal morphology was achieved with a 50 mg/kg dose. Both 15 and 30 mg/kg doses of sarpogrelate partially preserved retinal function measured by ERG, whereas 40 and 50 mg/kg doses fully preserved retinal function. Additionally, a single administration of 50 mg/kg sarpogrelate was able to fully preserve both retinal morphology and function. Administration of

15 mg/kg of sarpogrelate and 1 mg/kg of 8-OH-DPAT together demonstrated an additive effect and fully preserved retinal morphology. CONCLUSIONS: A 5- or 1-day treatment with 50 mg/kg sarpogrelate can completely protect the retina of BALB/c mice from light-induced retinopathy. Partial protection can be achieved with lower doses starting at 15 mg/kg and protection increases in a dose-dependent manner. Treatment with low doses of sarpogrelate and 8-OH-DPAT elicits an additive effect that results in full protection of retinal morphology.

Turner, E. H. (2015). From the FDA, we still hear mostly thunderous silence. *BMJ (Clinical Research Ed.), 351*, h3763.

van Dijk, E. H., van Herpen, C. M., Marinkovic, M., Haanen, J. B., Amundson, D., Luyten, G. P., et al. (2015). Serous retinopathy associated with mitogen-activated protein kinase kinase inhibition (binimetinib) for metastatic cutaneous and uveal melanoma. *Ophthalmology,*
PURPOSE: To analyze the clinical characteristics of a serous retinopathy associated with mitogen-activated protein kinase kinase (MEK) inhibition with binimetinib treatment for metastatic cutaneous melanoma (CM) and uveal melanoma (UM), and to determine possible pathogenetic mechanisms that may lead to this retinopathy. DESIGN: Prospective observational, cohort-based, cross-sectional study. PARTICIPANTS: Thirty CM patients and 5 UM patients treated with the MEK inhibitor binimetinib (CM) or a combination of binimetinib and the protein kinase C inhibitor sotrastaurin (UM). METHODS: Extensive ophthalmic examination was performed, including Early Treatment of Diabetic Retinopathy Study best-corrected visual acuity, applanation tonometry, slit-lamp examination, indirect ophthalmoscopy, digital color fundus photography, and optical coherence tomography (OCT). In selected cases, additional examinations were performed, including visual field testing and electro-oculography (EOG). Blood samples were obtained from 3 CM patients and 3 UM patients to analyze the presence of autoantibodies against retinal and retinal pigment epithelium (RPE) proteins. MAIN OUTCOME MEASURES: Visual symptoms, visual acuity, fundus appearance, characteristics on OCT, fundus autofluorescence (FAF), and EOG. RESULTS: Six CM patients (20%) and 2 UM patients (40%) reported visual symptoms during the study. The median time to the onset of symptoms, which were all mild and transient, was 3.5 days (range, <1 hour to 3 weeks). On OCT, subretinal fluid (SRF) was detected in 77% of CM

patients and 60% of UM patients. In the 26 patients with SRF, the fovea was affected in 85%.

After the start of the medication, an EOG was performed in 19 eyes of 11 patients; 16 of these

eyes (84%) developed SRF on OCT. Fifteen of these eyes (94%) showed an abnormal Arden ratio

(<1.65). A broad pattern of anti-retinal antibodies was found in 3 CM patients and 2 UM patients

tested, whereas anti-RPE antibodies were detected in all 6 tested patients. CONCLUSIONS: A

time-dependent and reversible serous retinopathy can develop both in patients with metastatic

CM and UM treated with binimetinib. A minority of patients develop visual symptoms, which are

generally mild and transient. A cause of binimetinib-associated serous retinopathy may be

toxicity of medication, but autoantibodies also may be involved.

Vangelisti, G. R. (2003). Training in rural surgery: A resident's perspective. *Bulletin of the American College of Surgeons, 88*(5), 18-20.

Vaughn, J. E., Gooley, T., Maziarz, R. T., Pulsipher, M. A., Bhatia, S., Maloney, D. G., et al. (2015). Pre-transplant comorbidity burden and post-transplant chronic graft-versus-host disease. *British Journal of Haematology,*

The Haematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) was designed as a predictor of non-relapse mortality after HCT. Chronic graft-versus-host disease (GVHD) contributes to mortality after HCT. Here, we investigated whether the HCT-CI could predict development of chronic GVHD or post-chronic GVHD mortality. We retrospectively analysed data from 2909 patients treated with allogeneic HCT for malignant and non-malignant haematological conditions at four institutions. In Cox regression models adjusted for potential confounders, increasing HCT-CI was not statistically significantly associated with the development of chronic GVHD [hazard ratio (HR) = 1.02, P = 0.34]. Yet, the index was associated with an increased risk of non-relapse mortality (HR = 1.29, P < 0.0001) as well as overall mortality (HR = 1.25, P < 0.001) following the development of chronic GVHD. The association between HCT-CI and post-chronic GVHD mortality was similar regardless of donor type or stem cell source. HCT-CI scores could be incorporated in the design of clinical trials for treatment of chronic GVHD.

Vaughn, J. E., Sorror, M. L., Storer, B. E., Chauncey, T. R., Pulsipher, M. A., Maziarz, R. T., et al. (2015). Long-term sustained disease control in patients with mantle cell lymphoma with or

without active disease after treatment with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. *Cancer,*

BACKGROUND: Previously, early results were reported for allogeneic hematopoietic cell transplantation (HCT) after nonmyeloablative conditioning with 2 Gy of total body irradiation with or without fludarabine and/or rituximab in 33 patients with mantle cell lymphoma (MCL). METHODS: This study examined the outcomes of 70 patients with MCL and included extended follow-up (median, 10 years) for the 33 initial patients. Grafts were obtained from human leukocyte antigen (HLA)-matched, related donors (47%), unrelated donors (41%), and HLA antigen-mismatched donors (11%). RESULTS: The 5-year incidence of nonrelapse mortality was 28%. The relapse rate was 26%. The 5-year rates of overall survival (OS) and progression-free survival (PFS) were 55% and 46%, respectively. The 10-year rates of OS and PFS were 44% and 41%, respectively. Eighty percent of surviving patients were off immunosuppression at the last follow-up. The presence of relapsed or refractory disease at the time of HCT predicted a higher rate of relapse (hazard ratio [HR], 2.94; P = .05). Despite this, OS rates at 5 (51% vs 58%) and 10 years (43% vs 45%) were comparable between those with relapsed/refractory disease and those undergoing transplantation with partial or complete remission. A high-risk cytomegalovirus (CMV) status was the only independent predictor of worse OS (HR, 2.32; P = .02). A high-risk CMV status and a low CD3 dose predicted PFS (HR, 2.22; P = .03). CONCLUSIONS: Nonmyeloablative allogeneic HCT provides a long-term survival benefit for patients with relapsed MCL, including those with refractory disease or multiple relapses. Cancer 2015. (c) 2015 American Cancer Society.

Vaz, L. E., Kleinman, K. P., Lakoma, M. D., Dutta-Linn, M. M., Nahill, C., Hellinger, J., et al. (2015). Prevalence of parental misconceptions about antibiotic use. *Pediatrics, 136*(2), 221-231. BACKGROUND: Differences in antibiotic knowledge and attitudes between parents of Medicaid-insured and commercially insured children have been previously reported. It is unknown whether understanding has improved and whether previously identified differences persist. METHODS: A total of 1500 Massachusetts parents with a child <6 years old insured by a Medicaid managed care or commercial health plan were surveyed in spring 2013. We examined antibiotic-related knowledge and attitudes by using chi(2) tests. Multivariable modeling was used to assess current

sociodemographic predictors of knowledge and evaluate changes in predictors from a similar

survey in 2000. RESULTS: Medicaid-insured parents in 2013 (n = 345) were younger, were less

likely to be white, and had less education than those commercially insured (n = 353), P < .01.

Fewer Medicaid-insured parents answered questions correctly except for one related to bronchitis,

for which there was no difference (15% Medicaid vs 16% commercial, P < .66). More parents

understood that green nasal discharge did not require antibiotics in 2013 compared with 2000,

but this increase was smaller among Medicaid-insured (32% vs 22% P = .02) than commercially

insured (49% vs 23%, P < .01) parents. Medicaid-insured parents were more likely to request

unnecessary antibiotics in 2013 (P < .01). Multivariable models for predictors of knowledge or

attitudes demonstrated complex relationships between insurance status and sociodemographic

variables. CONCLUSIONS: Misconceptions about antibiotic use persist and continue to be more

prevalent among parents of Medicaid-insured children. Improvement in understanding has been

more pronounced in more advantaged populations. Tailored efforts for socioeconomically

disadvantaged populations remain warranted to decrease parental drivers of unnecessary

antibiotic prescribing.

Vera-Rodriguez, M., Chavez, S. L., Rubio, C., Reijo Pera, R. A., & Simon, C. (2015). Prediction model

for aneuploidy in early human embryo development revealed by single-cell analysis. *Nature*

Communications, 6

Aneuploidies are prevalent in the human embryo and impair proper development, leading to cell

cycle arrest. Recent advances in imaging and molecular and genetic analyses are postulated as

promising strategies to unveil the mechanisms involved in aneuploidy generation. Here we

combine time-lapse, complete chromosomal assessment and single-cell RT-qPCR to

simultaneously obtain information from all cells that compose a human embryo until the

approximately eight-cell stage (n=85). Our data indicate that the chromosomal status of

aneuploid embryos (n=26), including those that are mosaic (n=3), correlates with significant

differences in the duration of the first mitotic phase when compared with euploid embryos

(n=28). Moreover, gene expression profiling suggests that a subset of genes is differentially

expressed in aneuploid embryos during the first 30h of development. Thus, we propose that the

chromosomal fate of an embryo is likely determined as early as the pronuclear stage and may be

predicted by a 12-gene transcriptomic signature. © 2015, Nature Publishing Group. All rights reserved.

Verhoef, C., Singla, N., Moneta, G., Muir, W., Rijken, A., Lockstadt, H., et al. (2015). Fibrocaps for surgical hemostasis: Two randomized, controlled phase II trials. *The Journal of Surgical Research, 194*(2), 679-687.

BACKGROUND: Fibrocaps, a ready-to-use, dry-powder fibrin sealant containing human plasma-derived thrombin and fibrinogen, is being developed as an adjunct for surgical hemostasis. MATERIALS AND METHODS: Safety and efficacy of Fibrocaps applied directly or by spray device, in combination with gelatin sponge, was compared with that of gelatin sponge-alone in two randomized, single-blind controlled trials: FC-002 US (United States) and FC-002 NL (the Netherlands). A total of 126 adult patients were randomized (Fibrocaps: n = 47 [FC-002 US], n = 39 [FC-002 NL]; gelatin sponge alone: n = 23 [FC-002 US], n = 17 [FC-002 NL). One bleeding site was treated during a surgical procedure (n = 125). Time to hemostasis (primary end point) was measured, with a 28-d safety follow-up. Four surgical indications included hepatic resection (n = 58), spinal procedures (n = 37), peripheral vascular procedures (n = 30), and soft tissue dissection (n = 1). RESULTS: Mean (standard deviation) time to hemostasis was significantly shorter after Fibrocaps treatment than after gelatin sponge alone (FC-002 US: 1.9 [1.3] versus 4.8 min [3.1], P < 0.001; FC-002 NL: 2.2 [1.3] versus 4.4 min [3.1], P = 0.004). The incidence of hemostasis was greater after Fibrocaps compared with that of gelatin sponge alone within 3 min (FC-002 US: 83% versus 35%, P < 0.001; FC-002 NL: 77% versus 53%, P = 0.11), 5 min (94% versus 61%, P = 0.001; 95% versus 71%, P = 0.022), and 10 min (100% versus 78%, P = 0.003; 100% versus 82%, P = 0.025). Adverse events were consistent with surgical procedures performed and patients' underlying diseases and generally similar between treatment arms; most were mild or moderate in severity. Non-neutralizing antithrombin antibodies were detected in 5% of Fibrocaps-treated patients on day 29. CONCLUSIONS: Fibrocaps had good safety and efficacy profiles, supporting continuing clinical development as a novel fibrin sealant.

Weintraub, D., Simuni, T., Caspell-Garcia, C., Coffey, C., Lasch, S., Siderowf, A., et al. (2015). Cognitive performance and neuropsychiatric symptoms in early, untreated parkinson's disease.

Movement Disorders, 30(7), 919-927.

This study was undertaken to determine the prevalence and correlates of cognitive impairment (CI) and neuropsychiatric symptoms (NPS) in early, untreated patients with Parkinson's disease (PD). Background: Both CI and NPS are common in PD and impact disease course and quality of life. However, limited knowledge is available about cognitive abilities and NPS. Methods: Parkinson's Progression Markers Initiative (PPMI) is a multi-site study of early, untreated PD patients and healthy controls (HCs), the latter with normal cognition. At baseline, participants were assessed with a neuropsychological battery and for symptoms of depression, anxiety, impulse control disorders (ICDs), psychosis, and apathy. Results: Baseline data of 423 PD patients and 196 HCs yielded no between-group differences in demographic characteristics. Twenty-two percent of PD patients met the PD-recommended screening cutoff for CI on the Montral Cognitive Assessment (MoCA), but only 9% met detailed neuropsychological testing criteria for mild cognitive impairment (MCI)-level impairment. The PD patients were more depressed than HCs (P<0.001), with twice as many (14% vs. 7%) meeting criteria for clinically significant depressive symptoms. The PD patients also experienced more anxiety (P<0.001) and apathy (P<0.001) than HCs. Psychosis was uncommon in PD (3%), and no between-group difference was seen in ICD symptoms (P=0.51). Conclusions: Approximately 10% of PD patients in the early, untreated disease state met traditional criteria of CI, which is a lower frequency compared with previous studies. Multiple dopaminergic-dependent NPS are also more common in these patients compared with the general population, but others associated with dopamine replacement therapy are not or are rare. Future analyses of this cohort will examine biological predictors and the course of CI and NPS. © 2015 International Parkinson and Movement Disorder Society.

Williams, C. N., Riva-Cambrin, J., Presson, A. P., & Bratton, S. L. (2015). Hyponatremia and poor cognitive outcome following pediatric brain tumor surgery. *Journal of Neurosurgery.Pediatrics, 15*(5), 480-487.

OBJECT: Pediatric intracranial neoplasms are common and cause substantial neurological morbidity. Postoperative hyponatremia is also common and may exacerbate neurological injury. The authors performed an exploratory analysis to evaluate an exposure-response relationship

between hyponatremia severity and cognitive function at discharge. METHODS: A retrospective cohort of patients 0-19 years old who underwent a first intracranial neoplasm surgery at a pediatric tertiary care hospital was reviewed. Outcome was assessed by Pediatric Cerebral Performance Category (PCPC) score of 1-6 at hospital discharge. Poor outcome was defined as PCPC score 3-6, corresponding to moderate or worse disability. RESULTS: Of 319 total children, 80 (25%) had poor outcomes. One hundred thirty-seven children (43%) had serum sodium concentrations </= 131-135 mEq/L and 39 (12%) had serum sodium concentrations </= 130 mEq/L. Lower nadir sodium concentration and longer duration of hyponatremia were significantly associated with worsening PCPC score (p < 0.001). Rapid sodium decreases and more hyponatremic episodes were also significantly associated with worsening PCPC score (p < 0.001). After adjustment for patient factors, tumor characteristics, and measures of sodium disruption, multivariable analysis revealed noncortical tumor locations and lower nadir sodium concentration (adjusted odds ratio 0.86, 95% confidence interval 0.78-0.95) were important independent risk factors for poor cognitive outcome. CONCLUSIONS: Neurocognitive disability and hyponatremia are common in children undergoing surgery for intracranial neoplasms. This study found a significant association between severity of hyponatremia and worsened cognitive outcome, with an apparent exposure-response relationship. These data support the need for careful postoperative monitoring of serum sodium. Further research is needed to determine if prevention and treatment of hyponatremia can improve outcomes in these children.

Williams, H. C., Apfelbacher, C., Chalmers, J. R., Schmitt, J., Simpson, E. L., Spuls, P. I., et al. (2015). Clearing up misunderstandings around core outcomes for atopic dermatitis. *British Journal of Dermatology,*

Winters-Stone, K. (2015). Exercise and cancer risk-how much is enough? *JAMA Oncology,*

Wong, J., Gallagher, K., & Zhang, J. (2015). TU-F-CAMPUS-T-02: Vernier picket fence test: A non-imaging method to localize the radiation isocenter with submillimeter accuracy. *Medical Physics, 42*(6), 3640.
PURPOSE: The purpose of this study is to propose a new non-imaging method to localize the radiation isocenter with submillimeter accuracy. METHODS: The Vernier picket fence (VPF) is a

multileaf collimator (MLC) picket fence sequence in which the fence spacing is 1/N smaller than the detector spacing of the QA phantom, where N is the magnification factor, typically set to 10 or 20. Similar to reading a Vernier caliper, the user can easily achieve the resolution of 1/N of the detector spacing by visually inspecting the maximum signal. To achieve higher accuracy, a Gaussian model was used to interpolate the peak position, which can fall between adjacent detectors. In two separate tests, precise MLC offsets and imprecise couch offsets were applied to a 2D detector array (MapCheck, Sun Nuclear Corp., Melbourne, Florida) to introduce setup errors. Two vertical VPF fields were delivered with collimator angles at 0 degrees and 90 degrees to detect the lateral and longitudinal setup errors, respectively. For a rotational QA phantom, an additional lateral VPF field is needed to detect the vertical setup error for three-dimensional capabilities. RESULTS: With N set to 20 and a detector spacing of 5 mm for MapCheck, the resolution of the VPF's visual analysis is 0.25 mm. With the Gaussian interpretation, the VPF can achieve an accuracy of 0.02 mm, as shown by the MLC offset test. The couch offset test measured the couch hysteresis and demonstrated that the setup error detected by the VPF differed from the ExacTrac (Brainlab AG, Feldkirchen, Germany) optical tracking by 0.055 mm in the lateral direction and 0.041 mm in the longitudinal direction on average. The VPF was also shown to be feasible in the vertical direction as well. CONCLUSION: This study verified the VPF as a non-imaging method to localize the radiation isocenter with submillimeter accuracy. Funding is in part by the Portland Chapter of the Achievement Rewards for College Scientists. The content is solely the responsibility of the authors, and does not necessarily represent the official views of the sponsors. The authors declare no conflict of interest.

Woodworth, G., Juve, A. M., Swide, C. E., & Maniker, R. (2015). An innovative approach to avoid reinventing the wheel: The anesthesia education toolbox. *Journal of Graduate Medical Education, 7*(2), 270-271.

Wu, M. D., Belcik, J. T., Qi, Y., Zhao, Y., Benner, C., Pei, H., et al. (2015). Abnormal regulation of microvascular tone in a murine model of sickle cell disease assessed by contrast ultrasound. *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography,*

BACKGROUND: Microvascular dysregulation, abnormal rheology, and vaso-occlusive events play a role in the pathophysiology of sickle cell disease (SCD). The aim of this study was to test the hypothesis that abnormalities in skeletal muscle perfusion in a murine model of SCD could be parametrically assessed by quantitative contrast-enhanced ultrasound perfusion imaging. METHODS: A murine model of moderate SCD without anemia produced by homozygous beta-globin deletion replaced by human betas-globin transgene (NY1DD-/-; n = 18), heterozygous transgene replacement (NY1DD+/-; n = 19), and C57Bl/6 control mice (n = 14) was studied. Quantitative contrast-enhanced ultrasound of the proximal hindlimb skeletal muscle was performed at rest and during contractile exercise (2 Hz). Time-intensity data were analyzed to measure microvascular blood volume (MBV), microvascular blood transit rate (beta), and microvascular blood flow. Erythrocyte deformability was measured by elongation at various rotational shears. RESULTS: At rest, muscle MBV was similar between strains, whereas beta was significantly (P = .0015, analysis of variance) reduced to a similar degree in NY1DD-/- and NY1DD+/- compared with wild-type mice (0.24 +/- 0.10, 0.16 +/- 0.07, and 0.34 +/- 0.14 sec-1, respectively), resulting in a reduction in microvascular blood flow. During contractile exercise, there were no groupwise differences in beta (1.43 +/- 0.67, 1.09 +/- 0.42, and 1.36 +/- 0.49 sec-1 for NY1DD-/-, NY1DD+/-, and wild-type mice, respectively) or in microvascular blood flow or MBV. Erythrocyte deformability at high shear stress (>/=5 Pa) was mildly reduced in both transgenic groups, although it was not correlated with blood flow or beta. CONCLUSIONS: Contrast-enhanced ultrasound in skeletal muscle revealed a lower microvascular blood transit rate in the NY1DD model of SCD and sickle trait but no alterations in MBV. The abnormality in microvascular blood transit rate was likely due to vasomotor dysfunction, because it was abrogated by contractile exercise and at rest was only weakly related to erythrocyte deformability.

Wu, X., & Yan, Y. (2015). Markov Random Field Linear Regression. *2000 10th European Signal Processing Conference, EUSIPCO 2000, , 2015-March.* (March)

This paper outlines the Markov Random Field Linear Regression (MRFLR) algorithm, which combines the transformation-based adaptation and dependency-modeling technique together. The hypothesis is that the adaptation performance can be improved by explicitly modeling the

correlations among acoustic parameters and applying such constraints to the transformation-matrix estimation. The correlations are modeled by Markov Random Field, and the incorporation of the correlations is under the Maximum A Posteriori framework. Experimental results show that MRFLR has significant improvement over Maximum Likelihood Linear Regression when only small amounts of adaptation data are available. © 2000 EUSIPCO.

Wu, Y. P., Aspinwall, L. G., Michaelis, T. C., Stump, T., Kohlmann, W. G., & Leachman, S. A. (2015). Discussion of photoprotection, screening, and risk behaviors with children and grandchildren after melanoma genetic testing. *Journal of Community Genetics,*
The purpose of the current study was to examine changes in frequency of discussion about melanoma preventive behaviors among adults who received melanoma genetic test reporting and counseling and their children and grandchildren, correspondence of frequency of discussion with intentions, and content of discussions. Participants received CDKN2A/p16 testing and counseling (N = 24, 46 % p16-positive). Discussions about preventive behaviors were assessed before testing and 1 and 6 months post-testing. Intentions to discuss preventive behaviors and perceived preparedness to discuss risk were assessed post-testing. Open-ended questions assessed content of reported discussions. Discussion of preventive behaviors declined following test reporting, with more rapid decline reported by noncarriers. There was a large gap between the percentage of participants who intended to discuss preventive behaviors and who then reported discussions 1 and 6 months after counseling. Participants felt prepared to discuss melanoma risk but also suggested resources to facilitate discussions. Genetic test reporting and counseling alone did not sustain discussions about preventive behaviors for a hereditary cancer with children and grandchildren. The gap between intentions to have discussions and reported discussions has implications for augmentation of counseling to support at-risk families' discussions about preventive behaviors. © 2015 Springer-Verlag Berlin Heidelberg

Xie, F., Li, B. X., Kassenbrock, A., Xue, C., Wang, X., Qian, D. Z., et al. (2015). Identification of a potent inhibitor of CREB-mediated gene transcription with efficacious in vivo anticancer activity. *Journal of Medicinal Chemistry, 58*(12), 5075-5087.
Recent studies have shown that nuclear transcription factor cyclic adenosine monophosphate

response element binding protein (CREB) is overexpressed in many different types of cancers. Therefore, CREB has been pursued as a novel cancer therapeutic target. Naphthol AS-E and its closely related derivatives have been shown to inhibit CREB-mediated gene transcription and cancer cell growth. Previously, we identified naphthamide 3a as a different chemotype to inhibit CREB's transcription activity. In a continuing effort to discover more potent CREB inhibitors, a series of structural congeners of 3a was designed and synthesized. Biological evaluations of these compounds uncovered compound 3i (666-15) as a potent and selective inhibitor of CREB-mediated gene transcription (IC50 = 0.081 ± 0.04 µM). 666-15 also potently inhibited cancer cell growth without harming normal cells. In an in vivo MDA-MB-468 xenograft model, 666-15 completely suppressed the tumor growth without overt toxicity. These results further support the potential of CREB as a valuable cancer drug target. © 2015 American Chemical Society.

Xie, Y., Pope, B. A., & Hunter, A. J. (2015). Cotton fever: Does the patient know best? *Journal of General Internal Medicine,*

Fever and leukocytosis have many possible etiologies in injection drug users. We present a case of a 22-year-old woman with fever and leukocytosis that were presumed secondary to cotton fever, a rarely recognized complication of injection drug use, after an extensive workup. Cotton fever is a benign, self-limited febrile syndrome characterized by fevers, leukocytosis, myalgias, nausea and vomiting, occurring in injection drug users who filter their drug suspensions through cotton balls. While this syndrome is commonly recognized amongst the injection drug user population, there is a paucity of data in the medical literature. We review the case presentation and available literature related to cotton fever. © 2015 Society of General Internal Medicine

Yadava, M., & Bala, R. (2015). Electrophysiological correlates of cardiac sarcoidosis: An appraisal of current evidence. *Turk Kardiyoloji Dernegi Arsivi : Turk Kardiyoloji Derneginin Yayin Organidir, 43*(4), 392-401.

Cardiac sarcoidosis is an underdiagnosed condition that may be present in as many as 25% of patients with systemic sarcoidosis. It is associated with significant morbidity and mortality in affected individuals. The presentation of cardiac involvement in sarcoidosis includes sudden death in the absence of preceding symptoms, conduction disturbances, ventricular arrhythmias, and

heart failure. A scarcity of randomized data and a lack of prospective trials underlies the contention between experts on the most appropriate strategies for diagnosis and therapy. This review focuses on the electrophysiological sequelae of the disease, with an emphasis on current diagnostic guidelines, multimodality imaging for early detection, and the role of various therapeutic interventions. Multicentre collaboration is necessary to address the numerous unanswered questions pertaining to management of this disease.

Yamamoto, S., Zhong, J., Yancey, P. G., Zuo, Y., Linton, M. F., Fazio, S., et al. (2015). Atherosclerosis following renal injury is ameliorated by pioglitazone and losartan via macrophage phenotype. *Atherosclerosis, 242*(1), 56-64.

OBJECTIVE: Chronic kidney disease (CKD) amplifies atherosclerosis, which involves renin-angiotensin system (RAS) regulation of macrophages. RAS influences peroxisome proliferator-activated receptor-gamma (PPARgamma), a modulator of atherogenic functions of macrophages, however, little is known about its effects in CKD. We examined the impact of combined therapy with a PPARgamma agonist and angiotensin receptor blocker on atherogenesis in a murine uninephrectomy model. METHODS: Apolipoprotein E knockout mice underwent uninephrectomy (UNx) and treatment with pioglitazone (UNx + Pio), losartan (UNx + Los), or both (UNx + Pio/Los) for 10 weeks. Extent and characteristics of atherosclerotic lesions and macrophage phenotypes were assessed; RAW264.7 and primary peritoneal mouse cells were used to examine pioglitazone and losartan effects on macrophage phenotype and inflammatory response. RESULTS: UNx significantly increased atherosclerosis. Pioglitazone and losartan each significantly reduced the atherosclerotic burden by 29.6% and 33.5%, respectively; although the benefit was dramatically augmented by combination treatment which lessened atherosclerosis by 55.7%. Assessment of plaques revealed significantly greater macrophage area in UNx + Pio/Los (80.7 +/- 11.4% vs. 50.3 +/- 4.2% in UNx + Pio and 57.2 +/- 6.5% in UNx + Los) with more apoptotic cells. The expanded macrophage-rich lesions of UNx + Pio/Los had more alternatively activated, Ym-1 and arginine 1-positive M2 phenotypes (Ym-1: 33.6 +/- 8.2%, $p < 0.05$ vs. 12.0 +/- 1.1% in UNx; arginase 1: 27.8 +/- 0.9%, $p < 0.05$ vs. 11.8 +/- 1.3% in UNx). In vitro, pioglitazone alone and together with losartan was more effective than losartan alone in dampening lipopolysaccharide-induced cytokine production, suppressing M1 phenotypic change while

enhancing M2 phenotypic change. CONCLUSION: Combination of pioglitazone and losartan is more effective in reducing renal injury-induced atherosclerosis than either treatment alone. This benefit reflects mitigation in macrophage cytokine production, enhanced apoptosis, and a shift toward an anti-inflammatory phenotype.

Yan, J., Ayer, T., Keskinocak, P., & Caughey, A. B. (2015). Preference-sensitive risk-cutoff values for prenatal-integrated screening test for down syndrome. *Prenatal Diagnosis, 35*(7), 645-651. Objective: For a pregnant woman considering prenatal screening for early detection of Down Syndrome (DS), there are at least two major outcomes of interest: undetected DS live births and euploid procedure-related fetal losses. The risk-cutoff value of 1/270 has been commonly used for recommending a diagnostic test. The objective of this study was to assess the impact of women's preferences for different pregnancy outcomes on the optimal risk-cutoff values for integrated screening. Method: We built a Monte Carlo simulation model of 100000 singleton second-trimester pregnancies to assess the probabilities of DS live births and euploid procedure-related fetal losses for various risk-cutoff values. To capture how undesirable some women may view an undetected DS live birth relative to a euploid procedure-related fetal loss, we used a ratio W1:W2 of weights (penalties) assigned to these two adverse pregnancy outcomes. Results: As the relative weight changes, the optimal risk-cutoff value changes significantly. Conclusion: A one-size-fits-all risk-cutoff value, such as 1/270, may not always be the best choice, depending on the preferences of women. Preference-sensitive risk-cutoff values for DS screening have the potential to improve the pregnancy outcomes and patient satisfaction. © 2015 John Wiley & Sons, Ltd.

Yao, H., Goldman, D. C., Fan, G., Mandel, G., & Fleming, W. H. (2015). The corepressor Rcor1 is essential for normal myeloerythroid lineage differentiation. *Stem Cells (Dayton, Ohio),* Based on its physical interactions with histone-modifying enzymes, the transcriptional corepressor Rcor1 has been implicated in the epigenetic regulation blood cell development. Previously, we have demonstrated that Rcor1 is essential for the maturation of definitive erythroid cells and fetal survival. To determine the functional role of Rcor1 in steady-state hematopoiesis in the adult, we used a conditional knockout approach. Here, we show that the

loss of Rcor1 expression results in the rapid onset of severe anemia due to a complete, cell autonomous block in the maturation of committed erythroid progenitors. By contrast, both the frequency of megakaryocyte progenitors and their capacity to produce platelets were normal. Although the frequency of common lymphoid progenitors and T cells was not altered, B cells were significantly reduced and showed increased apoptosis. However, Rcor1-deficient bone marrow sustained normal levels of B-cells following transplantation, indicating a non-cell autonomous requirement for Rcor1 in B-cell survival. Evaluation of the myelomonocytic lineage revealed an absence of mature neutrophils and a significant increase in the absolute number of monocytic cells. Rcor1-deficient monocytes were less apoptotic and showed approximately 100-fold more colony-forming activity than their normal counterparts, but did not give rise to leukemia. Moreover, Rcor1- / - monocytes exhibited extensive, cytokine-dependent self-renewal and overexpressed genes associated with hematopoietic stem/progenitor cell expansion including Gata2, Meis1, and Hoxa9. Taken together, these data demonstrate that Rcor1 is essential for the normal differentiation of myeloerythroid progenitors and for appropriately regulating self-renewal activity in the monocyte lineage. Stem Cells 2015.

Yki-Jarvinen, H., Bergenstal, R. M., Bolli, G. B., Ziemen, M., Wardecki, M., Muehlen-Bartmer, I., et al. (2015). Glycaemic control and hypoglycaemia with new insulin glargine 300 U/mL versus glargine 100 U/mL in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs (EDITION 2 randomised 12-month trial including 6-month extension). *Diabetes, Obesity & Metabolism,*

AIMS: To compare the efficacy and safety of new insulin glargine 300 U/mL (Gla-300) with glargine 100 U/mL (Gla-100) over 12 months of treatment in people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs (OADs). MATERIALS AND METHODS: EDITION 2 (NCT01499095) was a randomised, 6-month, multicentre, open-label, two-arm, phase 3a study investigating once-daily Gla-300 versus Gla-100, plus OADs (excluding sulphonylurea), with a 6-month safety extension. RESULTS: Similar numbers of participants in each group completed 12 months of treatment (Gla-300, 315 [78%]; Gla-100, 314 [77%]). Reduction in HbA1c was maintained through 12 months with both treatments (least squares (LS) mean [SE] change from baseline -0.55 [0.06] % for Gla-300 and -0.50 [0.06] % for Gla-100; LS mean difference -0.06

[95% CI: -0.22 to 0.10] %). A significant relative reduction of 37% in annualised rate of nocturnal confirmed (/=1 event (relative risk 0.84 [0.71 to 0.99]). Severe hypoglycaemia was infrequent. Weight gain was significantly lower with Gla-300 than Gla-100 (LS mean difference -0.7 [95% CI: -1.3 to -0.2] kg, p = 0.009). Both treatments were well tolerated with a similar pattern of adverse events (incidence of 69% and 60% in the Gla-300 and Gla-100 groups). CONCLUSIONS: In people with type 2 diabetes treated with Gla-300 or Gla-100, and non-sulphonylurea OADs, glycaemic control was sustained over 12 months, with less nocturnal hypoglycaemia in the Gla-300 group.

Yuan, J., Wright, G., Rosenwald, A., Steidl, C., Gascoyne, R. D., Connors, J. M., et al. (2015). Identification of primary mediastinal large B-cell lymphoma at nonmediastinal sites by gene expression profiling. *The American Journal of Surgical Pathology,*
Mediastinal involvement is considered essential for the diagnosis of primary mediastinal large B-cell lymphoma (PMBL). However, we have observed cases of diffuse large B-cell lymphoma (DLBCL) with features of PMBL but without detectable mediastinal involvement. The goal was to assess our previously established gene expression profiling (GEP) signature for PMBL in classifying these cases. In a large series of DLBCL cases, we identified 24 cases with a GEP signature of PMBL, including 9 cases with a submission diagnosis of DLBCL consistent with PMBL (G-PMBL-P) and 15 cases with a submission diagnosis of DLBCL. The pathology reviewers agreed with the diagnosis in the 9 G-PMBL-P cases. Among the other 15 DLBCL cases, 11 were considered to be PMBL or DLBCL consistent with PMBL, 3 were considered to be DLBCL, and 1 case was a gray-zone lymphoma with features intermediate between DLBCL and classical Hodgkin lymphoma. All 9 G-PMBL-P and 9 of the 15 DLBCL cases (G-PMBL-M) had demonstrated mediastinal involvement at presentation. Interestingly, 6 of the 15 DLBCL cases (G-PMBL-NM) had no clinical or radiologic evidence of mediastinal involvement. The 3 subgroups of PMBL had otherwise similar clinical characteristics, and there were no significant differences in overall survival. Genetic alterations of CIITA and PDL1/2 were detected in 26% and 40% of cases, respectively, including 1 G-PMBL-NM case with gain of PDL1/2. In conclusion, PMBL can present as a nonmediastinal tumor without evidence of mediastinal involvement, and GEP offers a more precise diagnosis of PMBL.

Yun, H., Badley, J. W., Curtis, J. R., & Winthrop, K. (2015). Reply. *Arthritis Care and Research, 67*(7), 1041-1042.

Yun, H., Xie, F., Delzell, E., Chen, L., Levitan, E. B., Lewis, J. D., et al. (2015). Risk of hospitalised infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy. *Annals of the Rheumatic Diseases, 74*(6), 1065-1071. BACKGROUND: The risk of subsequent infections in rheumatoid arthritis (RA) patients who receive biologic therapy after a serious infection is unclear. OBJECTIVE: To compare the subsequent risk of hospitalised infections associated with specific biologic agents among RA patients previously hospitalised for infection while receiving anti-tumour necrosis factor (anti-TNF) therapy. METHODS: Using 2006-2010 Medicare data for 100% of beneficiaries with RA enrolled in Medicare, we identified patients hospitalised with an infection while on anti-TNF agents. Follow-up began 61 days after hospital discharge and ended at the earliest of: next infection, loss of Medicare coverage or 18 months after start of follow-up. We calculated the incidence rate of subsequent hospitalised infection for each biologic and used Cox regression to control for potential confounders. RESULTS: 10 794 eligible hospitalised infections among 10183 unique RA patients who contributed at least 1 day of biologic exposure during follow-up. We identified 7807 person-years of exposure to selected biologics--333 abatacept, 133 rituximab and 7341 anti-TNFs (1797 etanercept, 1405 adalimumab, 4139 infliximab)--and 2666 associated infections. Mean age across biologic exposure cohorts was 64-69 years. The crude incidence rate of subsequent hospitalised infection ranged from 27.1 to 34.6 per 100 person-years. After multivariable adjustment, abatacept (HR: 0.80, 95% CI 0.64 to 0.99) and etanercept (HR: 0.83, 95% CI 0.72 to 0.96) users had significantly lower risks of subsequent infection compared to infliximab users. CONCLUSIONS: Among RA patients who experienced a hospitalised infection while on anti-TNF therapy, abatacept and etanercept were associated with the lowest risk of subsequent infection compared to other biologic therapies.

Zakhar, J., Amrock, S. M., & Weitzman, M. (2015). Passive and active tobacco exposure and children's lipid profiles. *Nicotine & Tobacco Research : Official Journal of the Society for Research on Nicotine and Tobacco,*

INTRODUCTIONDespite reductions in smoking rates, exposure to cigarette smoke remains common among US children and adolescents. In adults, active smoking and secondhand smoke (SHS) exposure have been linked to adverse changes in lipid profiles and increases in inflammatory markers. Evidence that such changes are present before adulthood remains limited, and the extent to which active smoking and SHS exposure affect these cardiovascular measures in children has not been thoroughly assessed.METHODSWe employed data from 2,008 individuals aged 12-19 years from the 2005-2010 National Health and Nutrition Examination Survey (NHANES). Comparisons of the lipid and inflammatory marker levels among active smokers, those exposed to SHS (as determined by serum cotinine levels), and those unexposed to tobacco smoke were made using linear regression with multiple propensity score adjustment.RESULTSCompared to unexposed children, lipid and inflammatory marker profiles did not differ among those exposed to SHS exposure. Among active smokers, differences compared to unexposed children were observed in triglyceride levels (beta = 8.5 mg/dL, P = 0.01), the ratio of triglycerides to HDL (beta = 0.2, P = 0.045), and LDL-C (beta = -4.1mg/dL, P = 0.03), though these did not reach levels of confirmatory statistical significance.CONCLUSIONSAfter accounting for sociodemographic characteristics and medical comorbidities, serum lipids and markers of systemic inflammation were not associated with SHS exposure. Tobacco smoke exposure in children may require longer durations of compounded effect before serum lipid abnormalities are detected.

Zhang, J. (2015). MO-D-BRD-03: Radiobiology and commissioning of electronic brachytherapy for IORT. *Medical Physics, 42*(6), 3556.

Electronic brachytherapy (eBT) has seen an insurgence of manufacturers entering the US market for use in radiation therapy. In addition to the established interstitial, intraluminary, and intracavitary applications of eBT, many centers are now using eBT to treat skin lesions. It is important for medical physicists working with electronic brachytherapy sources to understand the basic physics principles of the sources themselves as well as the variety of applications for which they are being used. The calibration of the sources is different from vendor to vendor and the traceability of calibrations has evolved as new sources came to market. In 2014, a new air-kerma based standard was introduced by the National Institute of Standards and Technology (NIST) to

measure the output of an eBT source. Eventually commercial treatment planning systems should accommodate this new standard and provide NIST traceability to the end user. The calibration and commissioning of an eBT system is unique to its application and typically entails a list of procedural recommendations by the manufacturer. Commissioning measurements are performed using a variety of methods, some of which are modifications of existing AAPM Task Group protocols. A medical physicist should be familiar with the different AAPM Task Group recommendations for applicability to eBT and how to properly adapt them to their needs. In addition to the physical characteristics of an eBT source, the photon energy is substantially lower than from HDR Ir-192 sources. Consequently, tissue-specific dosimetry and radiobiological considerations are necessary when comparing these brachytherapy modalities and when making clinical decisions as a radiation therapy team. In this session, the physical characteristics and calibration methodologies of eBt sources will be presented as well as radiobiology considerations and other important clinical considerations. LEARNING OBJECTIVES: 1.To understand the basic principles of electronic brachytherapy and the various applications for which it is being used.2.To understand the physics of the calibration and commissioning for electronic brachytherapy sources3.To understand the unique radiobiology and clinical implementation of electronic brachytherapy systems for skin and IORT techniquesXoft, Inc. contributed funding toward development of the NIST electronic brachytherapy facility (Michael Mitch).The University of Wisconsin (Wesley Culberson) has received research support funding from Xoft, Inc. Zoubir Ouhib has received partial funding from Elekta Esteya.

Zhang, J., Benedek, G., Bodhankar, S., Lapato, A., Vandenbark, A. A., & Offner, H. (2015). IL-10 producing B cells partially restore E2-mediated protection against EAE in PD-L1 deficient mice. *Journal of Neuroimmunology, 285*, 129-136.

Women with multiple sclerosis (MS) often experience clinical improvement during pregnancy, indicating that sex hormones might have therapeutic effects in MS. Our previous studies have demonstrated that B cells and PD-L1 are crucial for E2 (17beta-estradiol)-mediated protection against experimental autoimmune encephalomyelitis (EAE). We here demonstrate that the transfer of IL-10(+) B cells into E2-treated PD-L1(-/-) mice after EAE induction could partially restore E2-mediated protection and decrease the frequency of pro-inflammatory cells in the CNS

compared to E2/saline treated PD-L1(-/-) mice. Hence, co-administration of IL-10(+) B cells and E2 might have a powerful therapeutic potential for treatment of EAE.

Zhi, Z., Cepurna, W., Johnson, E., Jayaram, H., Morrison, J., & Wang, R. K. (2015). Evaluation of the effect of elevated intraocular pressure and reduced ocular perfusion pressure on retinal capillary bed filling and total retinal blood flow in rats by OMAG/OCT. *Microvascular Research, 101*, 86-95. PURPOSE: To determine if retinal capillary filling is preserved in the face of acutely elevated intraocular pressure (IOP) in anesthetized rats, despite a reduction in total retinal blood flow (RBF), using optical microangiography/optical coherence tomography (OMAG/OCT). METHODS: OMAG provided the capability of depth-resolved imaging of the retinal microvasculature down to the capillary level. Doppler OCT was applied to measure the total RBF using an enface integration approach. The microvascular pattern, capillary density, and total RBF were monitored in vivo as the IOP was increased from 10 to 100mmHg in 10mmHg intervals and returned back to 10mmHg. RESULTS: In animals with mean arterial pressure (MAP) of 102+/-4mmHg (n=10), when IOP was increased from 0 to 100mmHg, the capillary density remained at or above 80% of baseline for the IOP up to 60mmHg [or ocular perfusion pressure (OPP) at 40mmHg]. This was then decreased, achieving 60% of baseline at IOP 70mmHg and OPP of 30mmHg. Total RBF was unaffected by moderate increases in IOP up to 30mmHg, beyond which total RBF decreased linearly, reaching 50% of baseline at IOP 60mmHg and OPP 40mmHg. Both capillary density and total RBF were totally extinguished at 100mmHg, but fully recovered when IOP returned to baseline. By comparison, a separate group of animals with lower MAP (mean=75+/-6mmHg, n=7) demonstrated comparable decreases in both capillary filling and total RBF at IOPs that were 20mmHg lower than in the initial group. Both were totally extinguished at 80mmHg, but fully recovered when IOP returned to baseline. Relationships of both parameters to OPP were unchanged. CONCLUSION: Retinal capillary filling and total RBF responses to IOP elevation can be monitored non-invasively by OMAG/OCT and both are influenced by OPP. Retinal capillary filling was relatively preserved down to a perfusion pressure of 40mmHg, despite a linear reduction in total RBF.

Zhou, Z. -., Ota, S., Deng, C., Akiyama, H., & Hurlin, P. J. (2015). Mutant activated FGFR3 impairs endochondral bone growth by preventing SOX9 downregulation in differentiating chondrocytes. *Human Molecular Genetics, 24*(6), 1764-1773.

Fibroblast growth factor receptor 3 (FGFR3) plays a critical role in the control of endochondral ossification, and bone growth and mutations that cause hyperactivation of FGFR3 are responsible for a collection of developmental disorders that feature poor endochondral bone growth. FGFR3 is expressed in proliferating chondrocytes of the cartilaginous growth plate but also in chondrocytes that have exited the cell cycle and entered the prehypertrophic phase of chondrocyte differentiation. Achondroplasia disorders feature defects in chondrocyte proliferation and differentiation, and the defects in differentiation have generally been considered to be a secondary manifestation of altered proliferation. By initiating a mutant activated knockin allele of FGFR3 (FGFR3K650E) that causes Thanatophoric Dysplasia Type II (TDII) specifically in prehypertrophic chondrocytes, we show that mutant FGFR3 induces a differentiation block at this stage independent of any changes in proliferation. The differentiation block coincided with persistent expression of SOX9, the master regulator of chondrogenesis, and reducing SOX9 dosage allowed chondrocyte differentiation to proceed and significantly improved endochondral bone growth in TDII. These findings suggest that a proliferation-independent and SOX9-dependent differentiation block is a key driving mechanism responsible for poor endochondral bone growth in achondroplasia disorders caused by mutations in FGFR3. © The Author 2014. Published by Oxford University Press. All rights reserved.

Zive, D. M., Fromme, E. K., Schmidt, T. A., Cook, J. N., & Tolle, S. W. (2015). Timing of POLST form completion by cause of death. *Journal of Pain and Symptom Management,*

CONTEXT: The Physician Orders for Life-Sustaining Treatment (POLST) paradigm allows health care professionals to document the treatment preferences of patients with advanced illness or frailty as portable and actionable medical orders. National standards encourage offering POLST orders to patients for whom clinicians would not be surprised if they died in the next year. OBJECTIVES: To determine the influence of cause of death on the timing of POLST form completion and on changes to POLST orders as death approaches. METHODS: This was a cohort study of 18,285 Oregon POLST Registry decedents who died in 2010-2011 matched to Oregon

death certificates RESULTS: The median interval between POLST completion and death was 6.4 weeks. Those dying of cancer had forms completed nearer death (median 5.1 weeks) than those with organ failure (10.6 weeks) or dementia (14.5 weeks) (P<0.001). Over 90% of final POLST forms indicated orders for no resuscitation and 65.1% listed orders for comfort measures only. Eleven percent of the sample had multiple registered forms during the two years preceding their death, with the form completed nearest to death more likely than earlier forms to have orders for no resuscitation and comfort measures only, although some later forms did have orders for more treatment. CONCLUSION: Over half of POLST forms were completed in the final two months of life. Cause of death influenced when POLST forms were completed. POLST forms changed in the two years preceding death, more frequently recording fewer life-sustaining treatment orders than the earlier form(s).

Zupancic, J. A., & Dukhovny, D. (2015). Resource distribution in neonatology: Beyond the pareto principle. *Archives of Disease in Childhood.Fetal and Neonatal Edition,*