References

Adams, K., Osmundsen, B., & Gregory, W. T. (2014). Does fibromyalgia influence symptom bother from pelvic organ prolapse? *International Urogynecology Journal and Pelvic Floor Dysfunction, 25*(5), 677-682.

Introduction and hypothesis: Determine if women with fibromyalgia report increased bother from pelvic organ prolapse compared with women without fibromyalgia. Methods: We performed a cross-sectional study of women with symptomatic prolapse on consultation with a private urogynecology practice within a 46-month period. After matching for age, women with a diagnosis of fibromyalgia were compared with a reference group of women without fibromyalgia. Demographic, POPQ examination, medical history, and pelvic floor symptom data (PFDI, PFIQ, and PISQ-12) were collected. Our primary outcomewas to compare the mean Pelvic Floor Distress Inventory (PFDI) scores of women with and without fibromyalgia. Results: The prevalence of fibromyalgia in women evaluated for initial urogynecology consultation during the study period was 114 out of 1,113 (7%). Women with fibromyalgia reported significantly higher symptom bother scores related to pelvic organ prolapse, defecatory dysfunction, urinary symptoms, and sexual function: PFDI (p=0.005), PFIQ (p=0.010), and PISQ (p=0.018). Women with fibromyalgia were found to have a higher BMI (p=0.008) and were more likely to report a history of sexual abuse, OR 3.1 (95% CI 1.3, 7.9), and have levator myalgia on examination, OR 3.8 (95% CI 1.5, 9.1). In a linear regression analysis, levator myalgia was found to be the significant factor associated with pelvic floor symptom bother. Conclusions: In women with symptomatic prolapse, fibromyalgia is associated with an increased risk of levator myalgia and 50% more symptom bother from pelvic floor disorders. © The International Urogynecological Association 2013.

Adamus, G. (2014). Mitochondrial heat shock protein 70: New target for optic neuritis therapy. *Investigative Ophthalmology & Visual Science, 55*(8), 5227-15178.

Aga, M., Bradley, J. M., Wanchu, R., Yang, Y. F., Acott, T. S., & Keller, K. E. (2014). Differential effects of caveolin-1 and -2 knockdown on aqueous outflow and altered extracellular matrix turnover in caveolin-silenced trabecular meshwork cells. *Investigative Ophthalmology & Visual*

Science, 55(9), 5497-5509.

PURPOSE: A single nucleotide polymorphism (SNP) identified between caveolin-1 (CAV1) and caveolin-2 (CAV2) on chromosome 7 is associated with glaucoma. One function of CAVs is endocytosis and recycling of extracellular matrix (ECM) components. Here, we generated CAV-silencing lentivirus to evaluate the effects on ECM turnover by trabecular meshwork (TM) cells and to measure the effect on outflow facility in anterior segment perfusion culture. METHODS: Short hairpin CAV1 and CAV2 silencing and control lentivirus were generated, characterized, and applied to anterior segments in perfusion culture. Colocalization of CAVs with various ECM molecules in TM cells was investigated using immunofluorescence and confocal microscopy. Western immunoblotting and fluorogenic-based enzyme activity assays were used to investigate ECM protein levels and degradation, respectively. RESULTS: Endogenous CAVs colocalized with cortactin at podosome- or invadopodia-like structures (PILS), which are areas of focal ECM degradation. In perfusion culture, outflow rates increased significantly in CAV1-silenced anterior segments, whereas outflow significantly decreased in CAV2-silenced anterior segments. Matrix metalloproteinase (MMP)2 and MMP14, and a disintegrin and metalloproteinase with thrombospondin motifs-4 (ADAMTS4) colocalized with both CAVs in TM cells. Protein levels and enzyme activities of MMP/ADAMTS4, fibronectin protein levels, actin stress fibers, and alpha-smooth muscle actin were all increased in CAV-silenced cells. CONCLUSIONS: Caveolin-mediated endocytosis is one mechanism by which TM cells can alter the physiological catabolism of ECM in order to change the composition of the outflow channels in the TM to regulate aqueous outflow resistance. Dysregulation of CAV function could contribute to the pathological changes in ECM that are observed in glaucoma.

Agarwal, A., MacKenzie, R. J., Eide, C. A., Davare, M. A., Watanabe-Smith, K., Tognon, C. E., et al. (2014). Functional RNAi screen targeting cytokine and growth factor receptors reveals oncorequisite role for interleukin-2 gamma receptor in JAK3-mutation-positive leukemia. *Oncogene,*

To understand the role of cytokine and growth factor receptor-mediated signaling in leukemia pathogenesis, we designed a functional RNA interference (RNAi) screen targeting 188 cytokine and growth factor receptors that we found highly expressed in primary leukemia specimens.

Using this screen, we identified interleukin-2 gamma receptor (IL2Rgamma) as a critical growth determinant for a JAK3A572V mutation-positive acute myeloid leukemia cell line. We observed that knockdown of IL2Rgamma abrogates phosphorylation of JAK3 and downstream signaling molecules, JAK1, STAT5, MAPK and pS6 ribosomal protein. Overexpression of IL2Rgamma in murine cells increased the transforming potential of activating JAK3 mutations, whereas absence of IL2Rgamma completely abrogated the clonogenic potential of JAK3A572V, as well as the transforming potential of additional JAK3-activating mutations such as JAK3M511I. In addition, mutation at the IL2Rgamma interaction site in the FERM domain of JAK3 (Y100C) completely abrogated JAK3-mediated leukemic transformation. Mechanistically, we found IL2Rgamma contributes to constitutive JAK3 mutant signaling by increasing JAK3 expression and phosphorylation. Conversely, we found that mutant, but not wild-type JAK3, increased the expression of IL2Rgamma, indicating IL2Rgamma and JAK3 contribute to constitutive JAK/STAT signaling through their reciprocal regulation. Overall, we demonstrate a novel role for IL2Rgamma in potentiating oncogenesis in the setting of JAK3-mutation-positive leukemia. In addition, our study highlights an RNAi-based functional assay that can be used to facilitate the identification of non-kinase cytokine and growth factor receptor targets for inhibiting leukemic cell growth.Oncogene advance online publication, 11 August 2014; doi:10.1038/onc.2014.243.

Ali, A., Ku, J. H., Suhler, E. B., Choi, D., & Rosenbaum, J. T. (2014). The course of retinal vasculitis. *The British Journal of Ophthalmology, 98*(6), 785-789.

AIMS: To determine if characteristics of retinal vasculitis correlate with ocular complications, or the response to different lines of treatment. MATERIALS AND METHODS: We performed a computerised database analysis of 56 patients evaluated for uveitis at the Casey Eye Institute from September 1985 until May 2010. All patients had non-infectious retinal vasculitis and at least 1 year of follow-up. RESULTS: Although occlusive vasculitis was rare, retinal neovascularisation occurred much more commonly in the occlusive vasculitis subgroup than among the non-occlusive vasculitis subgroup ($p<0.01$). Epiretinal membrane (ERM) was found more commonly in the retinal vasculitis patients who presented with cotton wool spots and intraretinal haemorrhage compared to retinal vasculitis patients who presented with sheathing noted on clinical examination ($p<0.01$). Smoking was significantly related to vision loss. Age at

presentation below 40 years correlated with therapy beyond oral corticosteroids CONCLUSIONS: The heterogeneity of retinal vasculitis should be considered in providing prognostic information. Neovascularisation occurs more commonly in occlusive retinal vasculitis, and ERM is diagnosed more frequently in conjunction with cotton wool spots and intraretinal haemorrhage rather than just vascular sheathing. Cigarette use predicts visual loss and patients who are relatively young often receive treatment beyond oral corticosteroids.

Alt, J. A., Smith, T. L., Schlosser, R. J., Mace, J. C., & Soler, Z. M. (2014). *Sleep and quality of life improvements after endoscopic sinus surgery in patients with chronic rhinosinusitis*

Background: Recent investigation has demonstrated that approximately 75% of patients with medically refractory chronic rhinosinusitis (CRS) report abnormal sleep quality, with strong correlation between worse sleep quality and more severe CRS disease severity. It remains unknown whether the treatment effect of endoscopic sinus surgery (ESS) for CRS results in appreciable sleep quality improvements. Methods: Adult patients (aged ≥18 years) with a current diagnosis of recalcitrant chronic rhinosinusitis (CRS), who voluntarily elected ESS as the next treatment modality (n = 301), were prospectively evaluated within 4 academic, tertiary care centers using treatment outcome instruments: the Rhinosinusitis Disability Index, the 22-item Sinonasal Outcome Test, the 2-item Patient Health Questionnaire, and the Pittsburgh Sleep Quality Index (PSQI) both before and after ESS. Results: Seventy-two percent (72%) of patients with CRS were found to have poor sleep (PSQI > 5) at baseline with a mean (standard deviation) global PSQI score of 9.4 (4.6). Surgery improved overall mean global PSQI scores (by 2.2 points), and all 7 subdomain scores of the PSQI. Similarly, the odds of good sleep quality (PSQI ≤ 5) in patients treated with sinus surgery increased significantly (odds ratio [OR] 5.94; 95% confidence interval [CI], 3.06 to 11.53; p < 0.001). Stepwise multivariate linear regression found that acetylsalicylic acid (ASA) intolerance (β [standard error], -1.94 [0.93]; 95% CI, -3.77 to -0.11; p = 0.038), history of prior sinus surgery (β [standard error], 1.10 (0.54); 95% CI, 0.03 to 2.16; p = 0.044), and frontal sinusotomy (β [standard error], -1.03 [0.62]; 95% CI, -2.26 to 0.20; p = 0.099) were found to significantly associate with improvement in PSQI sleep scores. Conclusion: Among patients with CRS, reduced sleep quality, poor disease-specific quality of life, and greater disease severity were improved following ESS.

Althoff, T., Hibbs, R. E., Banerjee, S., & Gouaux, E. (2014). X-ray structures of GluCl in apo states reveal a gating mechanism of cys-loop receptors. *Nature, 512*(7514), 333-337.

Cys-loop receptors are neurotransmitter-gated ion channels that are essential mediators of fast chemical neurotransmission and are associated with a large number of neurological diseases and disorders, as well as parasitic infections. Members of this ion channel superfamily mediate excitatory or inhibitory neurotransmission depending on their ligand and ion selectivity. Structural information for Cys-loop receptors comes from several sources including electron microscopic studies of the nicotinic acetylcholine receptor, high-resolution X-ray structures of extracellular domains and X-ray structures of bacterial orthologues. In 2011 our group published structures of the Caenorhabditis elegans glutamate-gated chloride channel (GluCl) in complex with the allosteric partial agonist ivermectin, which provided insights into the structure of a possibly open state of a eukaryotic Cys-loop receptor, the basis for anion selectivity and channel block, and the mechanism by which ivermectin and related molecules stabilize the open state and potentiate neurotransmitter binding. However, there remain unanswered questions about the mechanism of channel opening and closing, the location and nature of the shut ion channel gate, the transitions between the closed/resting, open/activated and closed/desensitized states, and the mechanism by which conformational changes are coupled between the extracellular, orthosteric agonist binding domain and the transmembrane, ion channel domain. Here we present two conformationally distinct structures of C. elegans GluCl in the absence of ivermectin. Structural comparisons reveal a quaternary activation mechanism arising from rigid-body movements between the extracellular and transmembrane domains and a mechanism for modulation of the receptor by phospholipids.

Anand, S., & Coussens, L. M. (2014). Manipulating microRNAs to regulate macrophage polarization in gliomas. *Journal of the National Cancer Institute, 106*(8), 10.1093/jnci/dju230. Print 2014 Aug.

Andreisek, G., Deyo, R. A., Jarvik, J. G., Porchet, F., Winklhofer, S. F. X., & Steurer, J. (2014). Consensus conference on core radiological parameters to describe lumbar stenosis - an initiative for structured reporting. *European Radiology,*

Purpose To define radiological criteria and parameters as a minimum standard in a structured

radiological report for patients with lumbar spinal stenosis (LSS) and to identify criteria and parameters for research purposes. Material and methods All available radiological criteria and parameters for LSS were identified using systematic literature reviews and a Delphi survey. We invited to the consensus meeting, and provided data, to 15 internationally renowned experts from different countries. During the meeting, these experts reached consensus in a structured and systematic discussion about a core list of radiological criteria and parameters for standard reporting. Results We identified a total of 27 radiological criteria and parameters for LSS. During the meeting, the experts identified five of these as core items for a structured report. For central stenosis, these were "compromise of the central zone" and "relation between fluid and cauda equina". For lateral stenosis, the group agreed that "nerve root compression in the lateral recess" was a core item. For foraminal stenosis, we included "nerve root impingement" and "compromise of the foraminal zone". Conclusion As a minimum standard, five radiological criteria should be used in a structured radiological report in LSS. Other parameters are well suited for research. Key Points • The five most important radiological criteria for standard clinical reporting were selected• The five most important quantitative radiological parameters for research purposes were selected• These core criteria could help standardize the communication between health care providers © 2014 European Society of Radiology.

Andresen, E. M., Malmstrom, T. K., Schootman, M., Wolinsky, F. D., Miller, J. P., & Miller, D. K. (2013). Observer ratings of neighborhoods: Comparison of two methods. *BMC Public Health, 13*, 1024-2458-13-1024.

BACKGROUND: Although neighborhood characteristics have important relationships with health outcomes, direct observation involves imperfect measurement. The African American Health (AAH) study included two observer neighborhood rating systems (5-item Krause and 18-item AAH Neighborhood Assessment Scale [NAS]), initially fielded at two different waves. Good measurement characteristics were previously shown for both, but there was more rater variability than desired. In 2010 both measures were re-fielded together, with enhanced training and field methods implemented to decrease rater variability while maintaining psychometric properties. METHODS: AAH included a poor inner city and more heterogeneous suburban areas. Four interviewers rated 483 blocks, with 120 randomly-selected blocks rated by two interviewers. We

conducted confirmatory factor analysis of scales and tested the Krause (5-20 points), AAH 18-item NAS (0-28 points), and a previous 7-item and new 5-item versions of the NAS (0-17 points, 0-11 points). Retest reliability for items (kappa) and scales (Intraclass Correlation Coefficient [ICC]) were calculated overall and among pre-specified subgroups. Linear regression assessed interviewer effects on total scale scores and assessed concurrent validity on lung and lower body functions. Mismeasurement effects on self-rated health were also assessed. RESULTS: Scale scores were better in the suburbs than in the inner city. ICC was poor for the Krause scale (ICC=0.19), but improved if the retests occurred within 10 days (ICC=0.49). The 7- and 5-item NAS scales had better ICCs (0.56 and 0.62, respectively), and were higher (0.71 and 0.73) within 10 days. Rater variability for the Kraus and 5- and 7-item NAS scales was 1-3 points (compared to the supervising rater). Concurrent validity was modest, with residents living in worse neighborhood conditions having worse function. Unadjusted estimates were biased towards the null compared with measurement-error corrected estimates. CONCLUSIONS: Enhanced field protocols and rater training did not improve measurement quality. Specifically, retest reliability and interviewer variability remained problematic. Measurement error partially reduced, but did not eliminate concurrent validity, suggesting there are robust associations between neighborhood characteristics and health outcomes. We conclude that the 5-item AAH NAS has sufficient reliability and validity for further use. Additional research on the measurement properties of environmental rating methods is encouraged.

Armand, P., Kim, H. T., Logan, B. R., Wang, Z., Alyea, E. P., Kalaycio, M. E., et al. (2014). Validation and refinement of the disease risk index for allogeneic stem cell transplantation. *Blood, 123*(23), 3664-3671.

Because the outcome of allogeneic hematopoietic cell transplantation (HCT) is predominantly influenced by disease type and status, it is essential to be able to stratify patients undergoing HCT by disease risk. The Disease Risk Index (DRI) was developed for this purpose. In this study, we analyzed 13,131 patients reported to the Center for International Blood and Marrow Transplant Research who underwent HCT between 2008 and 2010. The DRI stratified patients into 4 groups with 2-year overall survival (OS) ranging from 64% to 24% and was the strongest prognostic factor, regardless of age, conditioning intensity, graft source, or donor type. A

randomly selected training subgroup of 9849 patients was used to refine the DRI, using a multivariable regression model for OS. This refined DRI had improved prediction ability for the remaining 3282 patients compared with the original DRI or other existing schemes. This validated and refined DRI can be used as a 4- or 3-group index, depending on the size of the cohort under study, for prognostication; to facilitate the interpretation of single-center, multicenter, or registry studies; to adjust center outcome data; and to stratify patients entering clinical trials that enroll patients across disease categories.

Arpan, I., Willcocks, R. J., Forbes, S. C., Finkel, R. S., Lott, D. J., Rooney, W. D., et al. (2014). Examination of effects of corticosteroids on skeletal muscles of boys with DMD using MRI and MRS. *Neurology,*

OBJECTIVE: To evaluate the effects of corticosteroids on the lower extremity muscles in boys with Duchenne muscular dystrophy (DMD) using MRI and magnetic resonance spectroscopy (MRS). METHODS: Transverse relaxation time (T2) and fat fraction were measured by MRI/MRS in lower extremity muscles of 15 boys with DMD (age 5.0-6.9 years) taking corticosteroids and 15 corticosteroid-naive boys. Subsequently, fat fraction was measured in a subset of these boys at 1 year. Finally, MRI/MRS data were collected from 16 corticosteroid-naive boys with DMD (age 5-8.9 years) at baseline, 3 months, and 6 months. Five boys were treated with corticosteroids after baseline and the remaining 11 served as corticosteroid-naive controls. RESULTS: Cross-sectional comparisons demonstrated lower muscle T2 and less intramuscular (IM) fat deposition in boys with DMD on corticosteroids, suggesting reduced inflammation/damage and fat infiltration with treatment. Boys on corticosteroids demonstrated less increase in IM fat infiltration at 1 year. Finally, T2 by MRI/MRS detected effects of corticosteroids on leg muscles as early as 3 months after drug initiation. CONCLUSIONS: These results demonstrate the ability of MRI/MRS to detect therapeutic effects of corticosteroids in reducing inflammatory processes in skeletal muscles of boys with DMD. Our work highlights the potential of MRI/MRS as a biomarker in evaluating therapeutic interventions in DMD.

Asgari, M., Bayestehtashk, A., & Shafran, I. (2013). Robust and accurate features for detecting and diagnosing autism spectrum disorders. *14th Annual Conference of the International Speech*

Communication Association, INTERSPEECH 2013, Lyon. pp. 191-194.

In this paper, we report experiments on the Interspeech 2013 Autism Challenge, which comprises of two subtasks - detecting children with ASD and classifying them into four subtypes. We apply our recently developed algorithm to extract speech features that overcomes certain weaknesses of other currently available algorithms [1, 2]. From the input speech signal, we estimate the parameters of a harmonic model of the voiced speech for each frame including the fundamental frequency (f0). From the fundamental frequencies and the reconstructed noise-free signal, we compute other derived features such as Harmonicto- Noise Ratio (HNR), shimmer, and jitter. In previous work, we found that these features detect voiced segments and speech more accurately than other algorithms and that they are useful in rating the severity of a subject's Parkinson's disease [3]. Here, we employ these features, along with standard features such as energy, cepstral, and spectral features. With these features, we detect ASD using a regression and identify the sub-type using a classifier. We find that our features improve the performance, measured in terms of unweighted average recall (UAR), of detecting autism spectrum disorder by 2.3% and classifying the disorder into four categories by 2.8% over the baseline results.

Asgari, M., Kiss, G., Van Santen, J., Shafran, I., & Song, X. (2014). Automatic measurement of affective valence and arousal in speech. *2014 IEEE International Conference on Acoustics, Speech, and Signal Processing, ICASSP 2014,* Florence. pp. 965-969.

Methods are proposed for measuring affective valence and arousal in speech. The methods apply support vector regression to prosodic and text features to predict human valence and arousal ratings of three stimulus types: speech, delexicalized speech, and text transcripts. Text features are extracted from transcripts via a lookup table listing per-word valence and arousal values and computing per-utterance statistics from the per-word values. Prediction of arousal ratings of delexicalized speech and of speech from prosodic features was successful, with accuracy levels not far from limits set by the reliability of the human ratings. Prediction of valence for these stimulus types as well as prediction of both dimensions for text stimuli proved more difficult, even though the corresponding human ratings were as reliable. Text based features did add, however, to the accuracy of prediction of valence for speech stimuli. We conclude that arousal of

speech can be measured reliably, but not valence, and that improving the latter requires better lexical features. © 2014 IEEE.

Asgari, M., & Shafran, I. (2013). Improving the accuracy and the robustness of harmonic model for pitch estimation. *14th Annual Conference of the International Speech Communication Association, INTERSPEECH 2013,* Lyon. pp. 1936-1940.

Accurate and robust estimation of pitch plays a central role in speech processing. Various methods in time, frequency and cepstral domain have been proposed for generating pitch candidates. Most algorithms excel when the background noise is minimal or for specific types of background noise. In this work, our aim is to improve the robustness and accuracy of pitch estimation across a wide variety of background noise conditions. For this we have chosen to adopt, the harmonic model of speech, a model that has gained considerable attention recently. We address two major weakness of this model. The problem of pitch halving and doubling, and the need to specify the number of harmonics. We exploit the energy of frequency in the neighborhood to alleviate halving and doubling. Using a model complexity term with a BIC criterion, we chose the optimal number of harmonics. We evaluated our proposed pitch estimation method with other state of the art techniques on Keele data set in terms of gross pitch error and fine pitch error. Through extensive experiments on several noisy conditions, we demonstrate that the proposed improvements provide substantial gains over other popular methods under different noise levels and environments. Copyright © 2013 ISCA.

Assaf, B. T., Mansfield, K. G., Strelow, L., Westmoreland, S. V., Barry, P. A., & Kaur, A. (2014). Limited dissemination and shedding of the UL128 complex-intact, UL/b'-defective rhesus cytomegalovirus strain 180.92. *Journal of Virology, 88*(16), 9310-9320.

The UL128 complex of human cytomegalovirus (CMV) is a major determinant of viral entry into epithelial and endothelial cells and a target for vaccine development. The UL/b' region of rhesus CMV contains several open reading frames, including orthologs of the UL128 complex. We recently showed that the coding content of the rhesus CMV (RhCMV) UL/b' region predicts acute endothelial tropism and long-term shedding in vivo in the rhesus macaque model of CMV infection. The laboratory-passaged RhCMV 180.92 strain has a truncated UL/b' region but an

intact UL128 complex. To investigate whether the presence of the UL128 complex alone was sufficient to confer endothelial and epithelial tropism in vivo, we investigated tissue dissemination and viral excretion following experimental RhCMV 180.92 inoculation of RhCMV-seronegative rhesus macaques. We show the presence of at least two virus variants in the RhCMV 180.92 infectious virus stock. A rare variant noted for a nontruncated wildtype- virus-like UL/b' region, rapidly emerged during in vivo replication and showed high-level replication in blood and tissues and excretion in urine and saliva, features similar to those previously reported in naturally occurring wild-type RhCMV infection. In contrast, the predominant truncated version of RhCMV 180.92 showed significantly lower plasma DNAemia and limited tissue dissemination and viral shedding. These data demonstrate that the truncated RhCMV 180.92 variant is attenuated in vivo and suggest that additional UL/b' genes, besides the UL128 complex, are required for optimal in vivo CMV replication and dissemination.

Atkins, K. M., Thomas, L. L., Barroso-Gonzalez, J., Thomas, L., Auclair, S., Yin, J., et al. (2014). The multifunctional sorting protein PACS-2 regulates SIRT1-mediated deacetylation of p53 to modulate p21-dependent cell-cycle arrest. *Cell Reports,*

SIRT1 regulates the DNA damage response by deacetylating p53, thereby repressing p53 transcriptional output. Here, we demonstrate that the sorting protein PACS-2 regulates SIRT1-mediated deacetylation of p53 to modulate the DNA damage response. PACS-2 knockdown cells failed to efficiently undergo p53-induced cell-cycle arrest in response to DNA damage. Accordingly, p53 acetylation was reduced both in PACS-2 knockdown cells and thymocytes from Pacs-2-/- mice, thereby blunting induction of the cyclin-dependent kinase inhibitor p21 (CDKN1A). The SIRT1 inhibitor EX-527 or SIRT1 knockdown restored p53 acetylation and p21 induction as well as p21-dependent cell-cycle arrest in PACS-2 knockdown cells. Trafficking studies revealed that cytoplasmic PACS-2 shuttled to the nucleus, where it interacted with SIRT1 and repressed SIRT1-mediated p53 deacetylation. Correspondingly, in vitro assays demonstrated that PACS-2 directly inhibited SIRT1-catalyzed p53 deacetylation. Together, these findings identify PACS-2 as an in vivo mediator of the SIRT1-p53-p21 axis that modulates the DNA damage response.

Bagby, G. C. (2012). *Aplastic anemia and related bone marrow failure states* Elsevier Inc.

Bailly, D. K., Boshkov, L. K., Zubair, M. M., Rogers, V. J., Lantz, G., Armsby, L., et al. (2014). Congenital cardiac lesions involving systolic flow abnormalities are associated with platelet dysfunction in children. *The Annals of Thoracic Surgery,*

BACKGROUND: Shear stress-induced platelet dysfunction (PD) is prevalent among adults with aortic stenosis. Our aim was to determine whether abnormal platelet function was associated with specific congenital cardiac lesions in children. METHODS: The charts of 407 children who had undergone cardiopulmonary bypass and had preoperative platelet function analysis were evaluated. Patients were assigned to 1 of 11 different lesion categories. Platelet dysfunction (PD) was defined as prolonged closure time (CT) as measured with a platelet function analyzer. Odds ratio (OR) estimates for prolonged CT were calculated for each lesion category. Mean CTs were compared with Tukey-Kramer separated means testing. Analysis of variance modeling was used to determine association between hematocrit value and CT. RESULTS: CT in patients with ventricular septal defects (VSD) and right ventricular outflow tract obstruction (RVOTO) lesions was prolonged. OR analysis found that patients with VSDs (OR, 2.46) or RVOTO (OR, 2.88) had at least a 95% probability of an abnormal CT. In contrast, patients with atrial septal defect (ASD), bidirectional Glenn procedure (BDG), and pulmonary insufficiency (PI) had a reduced probability of a prolonged CT ($p < 0.05$). A similar pattern was seen in parametric analysis comparing mean CTs across lesion categories. A lower preoperative hematocrit value was associated with prolonged CTs across all lesion types ($p < 0.05$). CONCLUSIONS: PD was common in children with congenital cardiac lesions involving systolic flow abnormalities and was uncommon among children with lesions having diastolic abnormalities. Lower preoperative hematocrit values were associated with prolonged CTs, suggesting subclinical bleeding secondary to excessive platelet shearing.

Balaji, S., Daga, A., Bradley, D. J., Etheridge, S. P., Law, I. H., Batra, A. S., et al. (2014). An international multicenter study comparing arrhythmia prevalence between the intracardiac lateral tunnel and the extracardiac conduit type of fontan operations. *Journal of Thoracic and Cardiovascular Surgery, 148*(2), 576-581.

Objective The study objective was to determine whether the extracardiac conduit Fontan confers an arrhythmia advantage over the intracardiac lateral tunnel Fontan. Methods This multicenter study of 1271 patients compared bradyarrhythmia (defined as need for pacing) and tachyarrhythmia (defined as needing antiarrhythmic therapy) between 602 patients undergoing the intracardiac Fontan and 669 patients undergoing the extracardiac Fontan. The median age at the time of the Fontan procedure was 2.1 years (interquartile range, 1.6-3.2 years) for the intracardiac group and 3.0 years (interquartile range, 2.4-3.9) for the extracardiac group (P 30 days) bradyarrhythmia occurred in 105 patients (18%) in the intracardiac group and 63 patients (9%) in the extracardiac group (P 30 days) tachyarrhythmia occurred in 58 patients (10%) in the intracardiac group and 23 patients (3%) in the extracardiac group (P <.0001). By multivariate analysis factoring time since surgery, more patients in the extracardiac group had early bradycardia (odds ratio, 2.9; 95% confidence interval, 1.8-4.6), with no difference in early tachycardia, late bradycardia, or late tachycardia. Conclusions Overall arrhythmia burden is similar between the 2 groups, but the extracardiac Fontan group had a higher incidence of early bradyarrhythmias. There was no difference in the incidence of late tachyarrhythmias over time between the 2 operations. Therefore, the type of Fontan performed should be based on factors other than an anticipated reduction in arrhythmia burden from the extracardiac conduit.

Balog, E. K., Hanson, J. L., & Blaschke, G. S. (2014). Teaching the essentials of "well-child care": Inspiring proficiency and passion. *Pediatrics, 134*(2), 206-209.

Barker, A. F., O'Donnell, A. E., Flume, P., Thompson, P. J., Ruzi, J. D., de Gracia, J., et al. (2014). Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): Two randomised double-blind, placebo-controlled phase 3 trials. *The Lancet.Respiratory Medicine,*

BACKGROUND: The clinical benefit of inhaled antibiotics in non-cystic fibrosis bronchiectasis has not been established in randomised controlled trials. We aimed to assess safety and efficacy of aztreonam for inhalation solution (AZLI) in patients with non-cystic fibrosis bronchiectasis and Gram-negative bacterial colonisation. METHODS: AIR-BX1 and AIR-BX2 were two double-blind,

multicentre, randomised, placebo-controlled phase 3 trials, which included patients aged 18 years or older who had bronchiectasis and history of positive sputum or bronchoscopic culture for target Gram-negative organisms. Patients were randomly assigned to receive either AZLI or placebo (1:1). Randomisation was done without stratification and the code was generated by a Gilead designee. In both studies, two 4-week courses of AZLI 75 mg or placebo (three-times daily; eFlow nebulizer) were each followed by a 4-week off-treatment period. Primary endpoint was change from baseline Quality of Life-Bronchiectasis Respiratory Symptoms scores (QOL-B-RSS) at 4 weeks. These trials are registered with ClinicalTrials.gov, numbers are NCT01313624 for AIR-BX1 and NCT01314716 for AIR-BX2. FINDINGS: We recruited participants from 47 ambulatory clinics for AIR-BX1 and 65 ambulatory clinics for AIR-BX2; studies were done between April 25, 2011, and July 1, 2013. In AIR-BX1, of the 348 patients screened, 134 were randomly assigned to receive AZLI and 132 to receive placebo. In AIR-BX2, of the 404 patients screened, 136 were randomly assigned to receive AZLI and 138 to receive placebo. The difference between AZLI and placebo for adjusted mean change from baseline QOL-B-RSS was not significant at 4 weeks (0.8 [95% CI -3.1 to 4.7], p=0.68) in AIR-BX1, but was significant (4.6 [1.1 to 8.2], p=0.011) in AIR-BX2. The 4.6 point difference in QOL-B-RSS after 4 weeks in AIR-BX2 was not deemed clinically significant. In both studies, treatment-related adverse events were more common in the AZLI group than in the placebo group, as were discontinuations from adverse events. The most commonly reported treatment-emergent adverse events were dyspnea, cough, and increased sputum. Each was more common for AZLI-treated than for placebo-treated patients, but the incidences were more balanced in AIR-BX2. INTERPRETATION: AZLI treatment did not provide significant clinical benefit in non-cystic fibrosis bronchiectasis, as measured by QOL-B-RSS, suggesting a continued need for placebo-controlled studies to establish the clinical benefit of inhaled antibiotics in patients with this disorder. FUNDING: Gilead Sciences.

Barmack, N. H., Qian, Z., & Yakhnitsa, V. (2014). Long-term climbing fibre activity induces transcription of microRNAs in cerebellar purkinje cells. *Philosophical Transactions of the Royal Society of London.Series B, Biological Sciences, 369*(1652), 20130508.

Synaptic activation of central neurons is often evoked by electrical stimulation leading to post-tetanic potentiation, long-term potentiation or long-term depression. Even a brief electrical

tetanus can induce changes in as many as 100 proteins. Since climbing fibre activity is often associated with cerebellar behavioural plasticity, we used horizontal optokinetic stimulation (HOKS) to naturally increase synaptic input to floccular Purkinje cells in mice for hours, not minutes, and investigated how this activity influenced the transcription of microRNAs, small non-coding nucleotides that reduce transcripts of multiple, complementary mRNAs. A single microRNA can reduce the translation of as many as 30 proteins. HOKS evoked increases in 12 microRNA transcripts in floccular Purkinje cells. One of these microRNAs, miR335, increased 18-fold after 24 h of HOKS. After HOKS stopped, miR335 transcripts decayed with a time constant of approximately 2.5 h. HOKS evoked a 28-fold increase in pri-miR335 transcripts compared with an 18-fold increase in mature miR335 transcripts, confirming that climbing fibre-evoked increases in miR335 could be attributed to increases in transcription. We used three screens to identify potential mRNA targets for miR335 transcripts: (i) nucleotide complementarity, (ii) detection of increased mRNAs following microinjection of miR335 inhibitors into the cerebellum, and (iii) detection of decreased mRNAs following HOKS. Two genes, calbindin and 14-3-3-theta, passed these screens. Transfection of N2a cells with miR335 inhibitors or precursors inversely regulated 14-3-3-theta transcripts. Immunoprecipitation of 14-3-3-theta co-immunoprecipitated PKC-gamma and GABAAgamma2. Knockdown of either 14-3-3-theta or PKC-gamma decreased the serine phosphorylation of GABAAgamma2, suggesting that 14-3-3-theta and PKC-gamma under the control of miR335 homeostatically regulate the phosphorylation and insertion of GABAAgamma2 into the Purkinje cell post-synaptic membrane.

Bascom, P. B. (2014). "Capital VE, cyrillicsmall o, cyrillicsmall de, cyrillicsmall a, cyrillic". *Journal of Palliative Medicine,*

Bayne, A. P., & Skoog, S. J. (2014). Nocturnal enuresis: An approach to assessment and treatment. *Pediatrics in Review / American Academy of Pediatrics, 35*(8), 327-335.

Bechtold, M. L., McClave, S. A., Palmer, L. B., Nguyen, D. L., Urben, L. M., Martindale, R. G., et al. (2014). The pharmacologic treatment of short bowel syndrome: New tricks and novel agents. *Current Gastroenterology Reports, 16*(7)

Short bowel syndrome (SBS) is a manifestation of massive resection of the intestines resulting in

severe fluid, electrolyte, and vitamin/mineral deficiencies. Diet and parenteral nutrition play a large role in the management of SBS; however, pharmacologic options are becoming more readily available. These pharmacologic agents focus on reducing secretions and stimulating intestinal adaptation. The choice of medication is highly dependent on the patient's symptoms, remaining anatomy, and risk versus benefit profile for each agent. This article focuses on common and novel pharmacologic medications used in SBS, including expert advice on their indications and use.

Beer, T. M., Armstrong, A. J., Rathkopf, D. E., Loriot, Y., Sternberg, C. N., Higano, C. S., et al. (2014). Enzalutamide in metastatic prostate cancer before chemotherapy. *New England Journal of Medicine, 371*(5), 424-433.

BACKGROUND: Enzalutamide is an oral androgen-receptor inhibitor that prolongs survival in men with metastatic castration-resistant prostate cancer in whom the disease has progressed after chemotherapy. New treatment options are needed for patients with metastatic prostate cancer who have not received chemotherapy, in whom the disease has progressed despite androgen-deprivation therapy. METHODS: In this double-blind, phase 3 study, we randomly assigned 1717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The coprimary end points were radiographic progression-free survival and overall survival. RESULTS: The study was stopped after a planned interim analysis, conducted when 540 deaths had been reported, showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% confidence interval [CI], 0.15 to 0.23; P<0.001). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P<0.001). The benefit of enzalutamide was shown with respect to all secondary end points, including the time until the initiation of cytotoxic chemotherapy (hazard ratio, 0.35), the time until the first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), the time until prostate-specific antigen (PSA) progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) (P<0.001 for all comparisons).

Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment. CONCLUSIONS: Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer. Copyright © 2014 Massachusetts Medical Society.

Bethoux, F., Rogers, H. L., Nolan, K. J., Abrams, G. M., Annaswamy, T. M., Brandstater, M., et al. (2014). The effects of peroneal nerve functional electrical stimulation versus ankle-foot orthosis in patients with chronic stroke: A randomized controlled trial. *Neurorehabilitation and Neural Repair, 28*(7), 688-697.

Background. Evidence supports peroneal nerve functional electrical stimulation (FES) as an effective alternative to ankle-foot orthoses (AFO) for treatment of foot drop poststroke, but few randomized controlled comparisons exist. Objective. To compare changes in gait and quality of life (QoL) between FES and an AFO in individuals with foot drop poststroke. Methods. In a multicenter randomized controlled trial (ClinicalTrials.gov #NCT01087957) with unblinded outcome assessments, 495 Medicare-eligible individuals at least 6 months poststroke wore FES or an AFO for 6 months. Primary endpoints: 10-Meter Walk Test (10MWT), a composite of the Mobility, Activities of Daily Living/Instrumental Activities of Daily Living, and Social Participation subscores on the Stroke Impact Scale (SIS), and device-related serious adverse event rate. Secondary endpoints: 6-Minute Walk Test, GaitRite Functional Ambulation Profile (FAP), Modified Emory Functional Ambulation Profile (mEFAP), Berg Balance Scale (BBS), Timed Up and Go, individual SIS domains, and Stroke-Specific Quality of Life measures. Multiply imputed intention-to-treat analyses were used with primary endpoints tested for noninferiority and secondary endpoints tested for superiority. Results. A total of 399 subjects completed the study. FES proved noninferior to the AFO for all primary endpoints. Both the FES and AFO groups improved significantly on the 10MWT. Within the FES group, significant improvements were found for SIS composite score, total mFEAP score, individual Floor and Obstacle course time scores of the mEFAP, FAP, and BBS, but again, no between-group differences were found. Conclusions. Use of FES is equivalent to the AFO. Further studies should examine whether FES enables better performance in tasks involving functional mobility, activities of daily living, and balance. © The Author(s) 2014.

Bhatia, N., Blauvelt, A., Brown, M., High, W., Leonardi, C. T., Rosen, T., et al. (2014). Updates on psoriasis and cutaneous oncology: Proceedings from the 2014 MauiDerm meeting. *Journal of Clinical and Aesthetic Dermatology, 7*(7 SUPPL.), S5-S22.

Bodhankar, S., Chen, Y., Lapato, A., Vandenbark, A. A., Murphy, S. J., & Offner, H. (2014). Targeting immune co-stimulatory effects of PD-L1 and PD-L2 might represent an effective therapeutic strategy in stroke. *Frontiers in Cellular Neuroscience, 8*, 228.

Stroke outcome is worsened by the infiltration of inflammatory immune cells into ischemic brains. Our recent study demonstrated that PD-L1- and to a lesser extent PD-L2-deficient mice had smaller brain infarcts and fewer brain-infiltrating cells vs. wild-type (WT) mice, suggesting a pathogenic role for PD-ligands in experimental stroke. We sought to ascertain PD-L1 and PD-L2-expressing cell types that affect T-cell activation, post-stroke in the context of other known co-stimulatory molecules. Thus, cells from male WT and PD-L-deficient mice undergoing 60 min of middle cerebral artery occlusion (MCAO) followed by 96 h of reperfusion were treated with neutralizing antibodies to study co-stimulatory and co-inhibitory interactions between CD80, cytotoxic T-lymphocyte antigen-4 (CTLA-4), PD-1, and PD-Ls that regulate CD8(+) and CD4(+) T-cell activation. We found that antibody neutralization of PD-1 and CTLA-4 signaling post-MCAO resulted in higher proliferation in WT CD8(+) and CD4(+) T-cells, confirming an inhibitory role of PD-1 and CTLA-4 on T-cell activation. Also, CD80/CD28 interactions played a prominent regulatory role for the CD8(+) T-cells and the PD-1/PD-L2 interactions were dominant in controlling the CD4(+) T-cell responses in WT mice after stroke. A suppressive phenotype in PD-L1-deficient mice was attributed to CD80/CTLA-4 and PD-1/PD-L2 interactions. PD-L2 was crucial in modulating CD4(+) T-cell responses, whereas PD-L1 regulated both CD8(+) and CD4(+) T-cells. To establish the contribution of PD-L1 and PD-L2 on regulatory B-cells (Bregs), infarct volumes were evaluated in male PD-L1- and PD-L2-deficient mice receiving IL-10(+) B-cells 4h post-MCAO. PD-L2- but not PD-L1-deficient recipients of IL-10(+) B-cells had markedly reduced infarct volumes, indicating a regulatory role of PD-L2 on Bregs. These results imply that PD-L1 and PD-L2 differentially control induction of T- and Breg-cell responses after MCAO, thus suggesting that selective targeting of PD-L1 and PD-L2 might represent a valuable therapeutic strategy in stroke.

Bogerd, H. P., Skalsky, R. L., Kennedy, E. M., Furuse, Y., Whisnant, A. W., Flores, O., et al. (2014). Replication of many human viruses is refractory to inhibition by endogenous cellular MicroRNAs. *Journal of Virology, 88*(14), 8065-8076.

The issue of whether viruses are subject to restriction by endogenous microRNAs (miRNAs) and/or by virus-induced small interfering RNAs (siRNAs) in infected human somatic cells has been controversial. Here, we address this question in two ways. First, using deep sequencing, we demonstrate that infection of human cells by the RNA virus dengue virus (DENV) or West Nile virus (WNV) does not result in the production of any virus-derived siRNAs or viral miRNAs. Second, to more globally assess the potential of small regulatory RNAs to inhibit virus replication, we used gene editing to derive human cell lines that lack a functional Dicer enzyme and that therefore are unable to produce miRNAs or siRNAs. Infection of these cells with a wide range of viruses, including DENV, WNV, yellow fever virus, Sindbis virus, Venezuelan equine encephalitis virus, measles virus, influenza A virus, reovirus, vesicular stomatitis virus, human immunodeficiency virus type 1, or herpes simplex virus 1 (HSV-1), failed to reveal any enhancement in the replication of any of these viruses, although HSV-1, which encodes at least eight Dicer-dependent viral miRNAs, did replicate somewhat more slowly in the absence of Dicer. We conclude that most, and perhaps all, human viruses have evolved to be resistant to inhibition by endogenous human miRNAs during productive replication and that dependence on a cellular miRNA, as seen with hepatitis C virus, is rare. How viruses have evolved to avoid inhibition by endogenous cellular miRNAs, which are generally highly conserved during metazoan evolution, remains to be determined. © 2014, American Society for Microbiology.

Boniface, K., & Yarris, L. M. (2014). Emergency ultrasound: Leveling the training and assessment landscape. *Academic Emergency Medicine, 21*(7), 803-805.

Bottomly, D., Wilmot, B., & McWeeney, S. K. (2014). Oligomask: A framework for assessing and removing the effect of genetic variants on microarray probes. *R Journal, 6*(1), 159-163.

As expression microarrays are typically designed relative to a reference genome, any individual genetic variant that overlaps a probe's genomic position can possibly cause a reduction in hybridization due to the probe no longer being a perfect match to a given sample's mRNA at that

locus. If the samples or groups used in a microarray study differ in terms of genetic variants, the results of the microarray experiment can be negatively impacted. The oligoMask package is an R/SQLite framework which can utilize publicly available genetic variants and works in conjunction with the oligo package to read in the expression data and remove microarray probes which are likely to impact a given microarray experiment prior to analysis. Tools are provided for creating an SQLite database containing the probe and variant annotations and for performing the commonly used RMA preprocessing procedure for Affymetrix microarrays.

Bredbenner, T. L., Mason, R. L., Havill, L. M., Orwoll, E. S., & Nicolella, D. P. (2014). Fracture risk predictions based on statistical shape and density modeling of the proximal femur. *Journal of Bone and Mineral Research, 29*(9), 2090-2100.

Increased risk of skeletal fractures due to bone mass loss is a major public health problem resulting in significant morbidity and mortality, particularly in the case of hip fractures. Current clinical methods based on two-dimensional measures of bone mineral density (areal BMD or aBMD) are often unable to identify individuals at risk of fracture. We investigated predictions of fracture risk based on statistical shape and density modeling (SSDM) methods using a case-cohort sample of individuals from the Osteoporotic Fractures in Men (MrOS) study. Baseline quantitative computed tomography (QCT) data of the right femur were obtained for 513 individuals, including 45 who fractured a hip during follow-up (mean 6.9 year observation, validated by physician review). QCT data were processed for 450 individuals (including 40 fracture cases) to develop individual models describing three-dimensional bone geometry and density distribution. Comparison of mean fracture and non-case models indicated complex structural differences that appear to be responsible for resistance to hip fracture. Logistic regressions were used to model the relation of baseline hip BMD and SSDM weighting factors to the occurrence of hip fracture. Area under the receiver operating characteristic (ROC) curve (AUC) for a prediction model based on weighting factors and adjusted by age was significantly greater than AUC for a prediction model based on aBMD and age (0.94 versus 0.83, respectively). The SSDM-based prediction model adjusted by age correctly identified 55% of the fracture cases (and 94.7% of the non-cases), whereas the clinical standard aBMD correctly identified 10% of the fracture cases (and 91.3% of the non-cases). SSDM identifies subtle

changes in combinations of structural bone traits (eg, geometric and BMD distribution traits) that appear to indicate fracture risk. Investigation of important structural differences in the proximal femur between fracture and no-fracture cases may lead to improved prediction of those at risk for future hip fracture. © 2014 American Society for Bone and Mineral Research. © 2014 American Society for Bone and Mineral Research.

Brian Fennerty, M. (2009). Acute diarrhea. *Decision Making in Medicine: An Algorithmic Approach: Third Edition,* , 202-203.

Brian Fennerty, M. (2009). Elevated serum iron. *Decision Making in Medicine: An Algorithmic Approach: Third Edition,* , 226-227.

Brian Fennerty, M. (2009). Irritable bowel syndrome. *Decision Making in Medicine: An Algorithmic Approach: Third Edition,* , 212-213.

Brian Fennerty, M. (2009). Positive fecal occult blood test (FOBT). *Decision Making in Medicine: An Algorithmic Approach: Third Edition,* , 216-217.

Brunye, T. T., Carney, P. A., Allison, K. H., Shapiro, L. G., Weaver, D. L., & Elmore, J. G. (2014). Eye movements as an index of pathologist visual expertise: A pilot study. *PloS One, 9*(8), e103447. A pilot study examined the extent to which eye movements occurring during interpretation of digitized breast biopsy whole slide images (WSI) can distinguish novice interpreters from experts, informing assessments of competency progression during training and across the physician-learning continuum. A pathologist with fellowship training in breast pathology interpreted digital WSI of breast tissue and marked the region of highest diagnostic relevance (dROI). These same images were then evaluated using computer vision techniques to identify visually salient regions of interest (vROI) without diagnostic relevance. A non-invasive eye tracking system recorded pathologists' (N = 7) visual behavior during image interpretation, and we measured differential viewing of vROIs versus dROIs according to their level of expertise. Pathologists with relatively low expertise in interpreting breast pathology were more likely to fixate on, and subsequently return to, diagnostically irrelevant vROIs relative to experts. Repeatedly fixating on the

distracting vROI showed limited value in predicting diagnostic failure. These preliminary results suggest that eye movements occurring during digital slide interpretation can characterize expertise development by demonstrating differential attraction to diagnostically relevant versus visually distracting image regions. These results carry both theoretical implications and potential for monitoring and evaluating student progress and providing automated feedback and scanning guidance in educational settings.

Bubalo, J. S., Kullar, R., & Maziarz, R. T. (2013). A pilot study of the efficacy and safety of empiric daptomycin therapy in oncology patients with fever and severe neutropenia. *Therapeutic Advances in Infectious Disease, 1*(6), 183-190.

OBJECTIVES: Patients with extended periods of time spent with low or absent absolute neutrophil counts (ANCs) are at risk for bacterial infections. Febrile neutropenia is a complication in this patient population, requiring administration of antibiotics. The use of daptomycin in treating patients with febrile neutropenia is not well described. Our objective was to describe the clinical course of febrile neutropenic patients that received daptomycin therapy. METHODS: This was an open-labeled, pilot study of 30 patients with documented febrile neutropenia treated with empiric daptomycin. Eligible patients received daptomycin 6 mg/kg/day, in addition to concomitant broad-spectrum antimicrobials. The Kaplan-Meier method was used to estimate the median days to reach an afebrile state and negative bacterial cultures. RESULTS: A total of 30 febrile neutropenic patients were enrolled and received daptomycin as part of an empiric antimicrobial regimen. All patients had severe neutropenia with ANC <100 cells/mm(3). Two patients were removed from study due to the development of pneumonia. Clinically, 87% patients improved on daptomycin in combination with Gram-negative coverage, with 73% of patients succeeding therapy. A total of 18 of 19 (95%) subjects with positive blood cultures had microbiological eradication, with the median time to reach an afebrile state of 4.3 days (range 1-13). Four patients were discontinued from daptomycin due to a suspected related adverse event or to clinical failure. CONCLUSIONS: This pilot study supports future evaluation of the use of empiric daptomycin therapy in combination with Gram-negative coverage compared with vancomycin in patients with neutropenic fever in a large, randomized controlled trial.

Burget, L., Motlíček, P., Grézl, F., & Jain, P. (2002). Distributed speech recognition. *Radioengineering, 11*(4), 12-16.

This article discusses possibilities of integrating speech technology into wireless technology, allowing voice input for wireless devices. Distributed speech recognition concept and activities related to its standardization are presented. First ETSI DSR MFCC based standard is described. Work on its extension to improve robustness resulting in new standard is also presented.

Burney, P., Kato, B., Janson, C., Mannino, D., Studnicka, M., Tan, W., et al. (2014). Chronic obstructive pulmonary disease mortality and prevalence: The associations with smoking and poverty: A BOLD analysis-authors' reply. *Thorax, 69*(9), 869-870.

Burwick, R. M. (2014). Indomethacin and antibiotics in examination-indicated cerclage: A randomized controlled trial. *Obstetrics and Gynecology, 124*(3), 637.

Buser, G. L., Gerona, R. R., Horowitz, B. Z., Vian, K. P., Troxell, M. L., Hendrickson, R. G., et al. (2014). Acute kidney injury associated with smoking synthetic cannabinoid. *Clinical Toxicology (Philadelphia, Pa.), 52*(7), 664-673.

Abstract Context and objectives. Synthetic cannabinoids are illegal drugs of abuse known to cause adverse neurologic and sympathomimetic effects. They are an emerging health risk: 11% of high school seniors reported smoking them during the previous 12 months. We describe the epidemiology of a toxicologic syndrome of acute kidney injury associated with synthetic cannabinoids, review the toxicologic and public health investigation of the cluster, and describe clinical implications of the cluster investigation. Materials and methods. Case series of nine patients affected by the toxicologic syndrome in Oregon and southwestern Washington during May-October 2012. Cases were defined as acute kidney injury (creatinine > 1.3 mg/dL) among persons aged 13-40 years without known renal disease who reported smoking synthetic cannabinoids. Toxicology laboratories used liquid chromatography and time-of-flight mass spectrometry to test clinical and product specimens for synthetic cannabinoids, their metabolites, and known nephrotoxins. Public health alerts informed clinicians, law enforcement, and the community about the cluster and the need to be alert for toxidromes associated with emerging drugs of abuse. Results. Patients were males aged 15-27 years (median, 18 years), with intense

nausea and flank or abdominal pain, and included two sets of siblings. Peak creatinine levels were 2.6-17.7 mg/dL (median, 6.6 mg/dL). All patients were hospitalized; one required dialysis; none died. No alternate causes of acute kidney injury or nephrotoxins were identified. Patients reported easily purchasing synthetic cannabinoids at convenience, tobacco, and adult bookstores. One clinical and 2 product samples contained evidence of a novel synthetic cannabinoid, XLR-11 ([1-(5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl)methanone). Discussion and conclusion. Whether caused by direct toxicity, genetic predisposition, or an as-yet unidentified nephrotoxin, this association between synthetic cannabinoid exposure and acute kidney injury reinforces the need for vigilance to detect new toxicologic syndromes associated with emerging drugs of abuse. Liquid chromatography and time-of-flight mass spectrometry are useful tools in determining the active ingredients in these evolving products and evaluating them for toxic contaminants.

Bylaska, E. J., Salter-Blanc, A. J., & Tratnyek, P. G. (2011). *One-electron reduction potentials from chemical structure theory calculations* American Chemical Society.

Many redox reactions of importance in aquatic chemistry involve elementary steps that occur by single-electron transfer (SET). This step is often the first and rate limiting step in redox reactions of environmental contaminants, so there has been a great deal of interest in the corresponding one-electron reduction potentials (E1). Although E1 can be obtained by experimental methods, calculation from first-principles chemical structure theory is becoming an increasingly attractive alternative. Sufficient data are now available to perform a critical assessment of these methods-and their results-for two types of contaminant degradation reactions: dehalogenation of chlorinated aliphatic compounds (CACs) and reduction of nitro aromatic compounds (NACs). Early datasets containing E1's for dehalogenation of CACs by dissociative SET contained a variety of errors and inconsistencies, but the preferred datasets show good agreement between values calculated from thermodynamic data and quantum mechanical models. All of the datasets with E1's for reduction of NACs by SET are relatively new, were calculated with similar methods, and yet yield a variety of systematic differences. Further analysis of these differences is likely to yield computational methods for E1's of NAC nitro reduction that are similar in reliability to those for CAC dechlorination. However, comparison of the E1 data compiled here with those calculated with

a more universal predictive model (like SPARC) highlight a number of challenges with implementation of models for predicting properties over a wide range of chemical structures. © 2011 American Chemical Society.

Castonguay, A., Zaidat, O., Novakovic, R., Gupta, R., Sun, C., Martin, C., et al. (2014). E-040 analysis of the SPAN-100 index as a predictor of clinical outcome in the post-marketing north american SOLITAIRE stent-retriever acute stroke registry. *Journal of Neurointerventional Surgery, 6 Suppl 1*, A56-2014-011343.107.

BACKGROUND: In light of the negative results of three randomised trials for endovascular acute ischemic stroke therapy, proper patient selection has become a critical area of focus for endovascular therapy. The Stroke Prognostication using Age and NIH Stroke Scale (SPAN) index, a score that combines age and NIHSS, demonstrated that SPAN-100 positive patients did not benefit from IV-tPA. Here, we sought to evaluate the predictive value of SPAN index in a real-life cohort of patients undergoing endovascular therapy. METHOD: Using data from the investigator-initiated, multicenter North American Solitaire Stent-Retriever Acute Stroke (NASA) Registry, the SPAN index was calculated for each patient (age plus NIHSS). A cohort of SPAN-100 positive (SPAN >/= 100) patients was identified and compared to SPAN-100 negative (SPAN /=2. Good clinical outcome was defined as a 90-day mRS /=2. Good clinical outcome was defined as a 90-day mRS /= 2) among the groups (p = 0.9). Only 26.5% (18/68) of patients in the SPAN-100 positive cohort had a 90-day mRS </= 2 vs. 47.1% (113/240) of those SPAN-100 negative (p = 0.002). Mortality was 50.0% (34/68) and 24.6% (59/240) in SPAN-100 positive and SPAN-100 negative, respectively. In a multivariate analysis, SPAN-100 positive was shown as an independent predictor of clinical outcome, with 2.5 times greater likelihood of worse outcome versus those with SPAN-100 negative (OR 2.5; 95% CI 1.3-5.1; p = 0.006). CONCLUSION: Analysis of the NASA Registry demonstrated that SPAN-100 positive is significantly associated with worse clinical outcome and higher mortality rate at 90 days compared to SPAN-100 negative patients. SPAN-100 was shown as an independent predictor of clinical outcome and may be useful tool in the selection of patients for endovascular therapy. DISCLOSURES: A. Castonguay: None. O. Zaidat: 1; C; Stryker Neurovascular, Covidien Neurovascular. 2; C; Covidien Neurovascular. R. Novakovic: None. R. Gupta: None. C. Sun: None. C. Martin: None. W.

Holloway: None. N. Mueller-Kronast: None. J. English: None. I. Linfante: None. G. Dabus: None. T. Malisch: None. F. Marden: None. H. Bozorgchami: None. A. Xavier: None. A. Rai: None. M. Froehler: None. A. Badruddin: None. T. Nguyen: None. M. Taqi: None. M. Abraham: None. V. Janardhan: None. H. Shaltoni: None. A. Yoo: None. A. Abou-Chebl: None.

Caughey, A. B. (2014). Can we safely reduce primary cesareans with greater patience? *Birth (Berkeley, Calif.), 41*(3), 217-219.

Caughey, A. B. (2014). Elective induction of labour is associated with decreased perinatal mortality and lower odds of caesarean section at 40 and 41 weeks. *Evidence-Based Medicine,*

Cawthon, P. M., Blackwell, T. L., Marshall, L. M., Fink, H. A., Kado, D. M., Ensrud, K. E., et al. (2014). Physical performance and radiographic and clinical vertebral fractures in older men. *Journal of Bone and Mineral Research, 29*(9), 2101-2108.

In men, the association between poor physical performance and likelihood of incident vertebral fractures is unknown. Using data from the MrOS study (N=5958), we describe the association between baseline physical performance (walking speed, grip strength, leg power, repeat chair stands, narrow walk [dynamic balance]) and incidence of radiographic and clinical vertebral fractures. At baseline and follow-up an average of 4.6 years later, radiographic vertebral fractures were assessed using semiquantitative (SQ) scoring on lateral thoracic and lumbar radiographs. Logistic regression modeled the association between physical performance and incident radiographic vertebral fractures (change in SQ grade =1 from baseline to follow-up). Every 4 months after baseline, participants self-reported fractures; clinical vertebral fractures were confirmed by centralized radiologist review of the baseline study radiograph and community-acquired spine images. Proportional hazards regression modeled the association between physical performance with incident clinical vertebral fractures. Multivariate models were adjusted for age, bone mineral density (BMD, by dual-energy X-ray absorptiometry [DXA]), clinical center, race, smoking, height, weight, history of falls, activity level, and comorbid medical conditions; physical performance was analyzed as quartiles. Of 4332 men with baseline and repeat radiographs, 192 (4.4%) had an incident radiographic vertebral fracture. With the exception of walking speed, poorer performance on repeat chair stands, leg power, narrow walk,

and grip strength were each associated in a graded manner with an increased risk of incident radiographic vertebral fracture (p for trend across quartiles <0.001). In addition, men with performance in the worst quartile on three or more exams had an increased risk of radiographic fracture (odds ratio [OR]=1.81, 95% confidence interval [CI] 1.33-2.45) compared with men with better performance on all exams. Clinical vertebral fracture (n =149 of 5813, 2.6%) was not consistently associated with physical performance. We conclude that poorer physical performance is associated with an increased risk of incident radiographic (but not clinical) vertebral fracture in older men.

Cefalu, W. T., Buse, J. B., Del Prato, S., Home, P. D., LeRoith, D., Nauck, M. A., et al. (2014). Beyond metformin: Safety considerations in the decision-making process for selecting a second medication for type 2 diabetes management: Reflections from a diabetes care editors' expert forum. *Diabetes Care, 37*(9), 2647-2659.

The trend toward personalized management of diabetes has focused attention on the differences among available pharmacological agents in terms of mechanisms of action, efficacy, and, most important, safety. Clinicians must select from these features to develop individualized therapy regimens. In June 2013, a nine-member Diabetes Care Editors' Expert Forum convened to review safety evidence for six major diabetes drug classes: insulin, sulfonylureas (SUs), thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose cotransporter 2 inhibitors. This article, an outgrowth of the forum, summarizes well-delineated and theoretical safety concerns related to these drug classes, as well as the panelists' opinions regarding their best use in patients with type 2 diabetes. All of the options appear to have reasonably wide safety margins when used appropriately. Those about which we know the most-metformin, SUs, insulin, and perhaps now also TZDs-are efficacious in most patients and can be placed into a basic initial algorithm. However, these agents leave some clinical needs unmet. Selecting next steps is a more formidable process involving newer agents that are understood less well and for which there are unresolved questions regarding risk versus benefit in certain populations. Choosing a specific agent is not as important as implementing some form of early intervention and advancing rapidly to some form of combination therapy as

needed. When all options are relatively safe given the benefits they confer, therapeutic decision making must rely on a personalized approach, taking into account patients' clinical circumstances, phenotype, pathophysiological defects, preferences, abilities, and costs.

Chan, A. K. W., Ferencik, M., Abbara, S., & Ghoshhajra, B. (2014). Low radiation coronary CT. *Current Cardiovascular Imaging Reports, 7*(9), 1-11.

With the increasing use of coronary computed tomography angiography (CCTA) as a noninvasive tool to evaluate for coronary artery disease, physicians who request, perform, or interpret these studies should be aware of the associated potential risks of ionizing radiation. This article provides an overview of radiation issues in CT, the risks of diagnostic-level ionizing radiation, and strategies that can be adopted to minimize exposure to radiation of patients undergoing CCTA.

Chattergoon, N. N., Louey, S., Stork, P., Giraud, G. D., & Thornburg, K. L. (2014). Unexpected maturation of PI3K and MAPK-ERK signaling in fetal ovine cardiomyocytes. *American Journal of Physiology.Heart and Circulatory Physiology,*

In the first 2/3 of gestation, ovine fetal cardiomyocytes undergo mitosis to increase cardiac mass and accommodate fetal growth. Thereafter, some myocytes continue to proliferate while others mature and terminally differentiate into binucleated cells. At term (145 days gestational age; dGA) about 60% of cardiomyocytes become binucleated and exit the cell cycle under hormonal control. Rising thyroid hormone (T3) levels near term (135 dGA) inhibit proliferation and stimulate maturation. However, the degree to which intracellular signaling patterns change with age in response to T3 is unknown. We hypothesized that in vitro activation of ERK, AKT, and p70S6K by two regulators of cardiomyocyte cell cycle activity, T3 and insulin like growth factor-1 (IGF-1), would be similar in cardiomyocytes at gestational ages, 100 and 135 dGA. IGF-1 and T3 each independently stimulated phosphorylation of ERK, AKT, and p70S6K in cells at both ages. In the younger mononucleated myocytes, the phosphorylation of ERK and AKT was reduced in the presence of IGF-1 and T3. However, the same hormone combination led to a dramatic two fold increase in the phosphorylation of these signaling proteins in the 135 dGA cardiomyocytes-even in cells that were not proliferating. In the older cells, both mono- and binucleated cells were

affected. Conclusion: Fetal ovine cardiomyocytes undergo profound maturation-related changes in signaling in response to T3 and IGF-1, but not to either factor alone. Differences in age-related response are likely to be related to milestones in fetal cardiac development as the myocardium prepares for ex utero life.

Chavez-Canales, M., Zhang, C., Soukaseum, C., Moreno, E., Pacheco-Alvarez, D., Vidal-Petiot, E., et al. (2014). WNK-SPAK-NCC cascade revisited: WNK1 stimulates the activity of the na-cl cotransporter via SPAK, an effect antagonized by WNK4. *Hypertension,*
The with-no-lysine (K) kinases, WNK1 and WNK4, are key regulators of blood pressure. Their mutations lead to familial hyperkalemic hypertension (FHHt), associated with an activation of the Na-Cl cotransporter (NCC). Although it is clear that WNK4 mutants activate NCC via Ste20 proline-alanine-rich kinase, the mechanisms responsible for WNK1-related FHHt and alterations in NCC activity are not as clear. We tested whether WNK1 modulates NCC through WNK4, as predicted by some models, by crossing our recently developed WNK1-FHHt mice (WNK1+/FHHt) with WNK4-/- mice. Surprisingly, the activated NCC, hypertension, and hyperkalemia of WNK1+/FHHt mice remain in the absence of WNK4. We demonstrate that WNK1 powerfully stimulates NCC in a WNK4-independent and Ste20 proline-alanine-rich kinase-dependent manner. Moreover, WNK4 decreases the WNK1 and WNK3-mediated activation of NCC. Finally, the formation of oligomers of WNK kinases through their C-terminal coiled-coil domain is essential for their activity toward NCC. In conclusion, WNK kinases form a network in which WNK4 associates with WNK1 and WNK3 to regulate NCC.

Chen, L., Durr, K. L., & Gouaux, E. (2014). X-ray structures of AMPA receptor-cone snail toxin complexes illuminate activation mechanism. *Science (New York, N.Y.), 345*(6200), 1021-1026.
AMPA-sensitive glutamate receptors are crucial to the structural and dynamic properties of the brain, to the development and function of the central nervous system, and to the treatment of neurological conditions from depression to cognitive impairment. However, the molecular principles underlying AMPA receptor activation have remained elusive. We determined multiple x-ray crystal structures of the GluA2 AMPA receptor in complex with a Conus striatus cone snail toxin, a positive allosteric modulator, and orthosteric agonists, at 3.8 to 4.1 angstrom resolution.

We show how the toxin acts like a straightjacket on the ligand-binding domain (LBD) "gating ring," restraining the domains via both intra- and interdimer cross-links such that agonist-induced closure of the LBD "clamshells" is transduced into an irislike expansion of the gating ring. By structural analysis of activation-enhancing mutants, we show how the expansion of the LBD gating ring results in pulling forces on the M3 helices that, in turn, are coupled to ion channel gating.

Cohen, D. J., Keller, S. R., Hayes, G. R., Dorr, D. A., Ash, J. S., & Sittig, D. F. (2014). Developing a model for understanding patient collection of observations of daily living: A qualitative meta-synthesis of the project HealthDesign program. *Personal and Ubiquitous Computing,*

We conducted a meta-synthesis of five different studies that developed, tested, and implemented new technologies for the purpose of collecting observations of daily living (ODL). From this synthesis, we developed a model to explain user motivation as it relates to ODL collection. We describe this model that includes six factors that motivate patients' collection of ODL data: usability, illness experience, relevance of ODL, information technology infrastructure, degree of burden, and emotional activation. We show how these factors can act as barriers or facilitators to the collection of ODL data and how interacting with care professionals and sharing ODL data may also influence ODL collection, health-related awareness, and behavior change. The model we developed and used to explain ODL collection can be helpful to researchers and designers who study and develop new, personal health technologies to empower people to improve their health.

Collins, P. W., Solomon, C., Sutor, K., Crispin, D., Hochleitner, G., Rizoli, S., et al. (2014). Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate. *British Journal of Anaesthesia,*

BACKGROUND: We aimed to create a theoretical tool to model the effect of three haemostatic agents containing fibrinogen (therapeutic plasma, cryoprecipitate, and fibrinogen concentrate) on the patient's plasma fibrinogen level. METHODS: A mathematical model was developed step-wise. The relationship between the amount of haemostatic agent and plasma fibrinogen level was plotted for each agent. A fibrinogen concentration simulator (FCSamount) was developed, where

the amount of haemostatic agent was calculated from patient characteristics, agent characteristics, and target plasma fibrinogen level. Refinements were introduced so that (i) FCSamount would account for in vivo fibrinogen recovery, (ii) circulatory volume would not increase ad infinitum with increasing amounts, and (iii) red blood cells would be included in the simulation if haematocrit decreased below a certain level. A second FCS (FCSlevel) was created to calculate fibrinogen levels resulting from specified amounts of haemostatic agents. RESULTS: Fibrinogen concentration in haemostatic agents has a critical impact on their ability to increase patients' fibrinogen levels. If the target plasma fibrinogen level approaches the concentration of the fibrinogen source, the required amounts increase exponentially; it is impossible to achieve a target above the concentration of the fibrinogen source. CONCLUSIONS: We successfully developed two theoretical tools answering the questions: 'How much therapeutic plasma, cryoprecipitate, or fibrinogen concentrate would be needed to achieve a specified target fibrinogen level?' and 'What would be the resultant fibrinogen level for a specified amount of haemostatic agent?' The current tools are not intended for clinical application, but they are potentially useful for educational purposes.

Collisson, E. A., Campbell, J. D., Brooks, A. N., Berger, A. H., Lee, W., Chmielecki, J., et al. (2014). Comprehensive molecular profiling of lung adenocarcinoma: The cancer genome atlas research network. *Nature, 511*(7511), 543-550.

Adenocarcinoma of the lung is the leading cause of cancer death worldwide. Here we report molecular profiling of 230 resected lung adenocarcinomas using messenger RNA, microRNA and DNA sequencing integrated with copy number, methylation and proteomic analyses. High rates of somatic mutation were seen (mean 8.9 mutations per megabase). Eighteen genes were statistically significantly mutated, including RIT1 activating mutations and newly described loss-of-function MGA mutations which are mutually exclusive with focal MYC amplification. EGFR mutations were more frequent in female patients, whereas mutations in RBM10 were more common in males. Aberrations in NF1, MET, ERBB2 and RIT1 occurred in 13% of cases and were enriched in samples otherwise lacking an activated oncogene, suggesting a driver role for these events in certain tumours. DNA and mRNA sequence from the same tumour highlighted splicing alterations driven by somatic genomic changes, including exon 14 skipping in MET mRNA in 4%

of cases. MAPK and PI(3)K pathway activity, when measured at the protein level, was explained by known mutations in only a fraction of cases, suggesting additional, unexplained mechanisms of pathway activation. These data establish a foundation for classification and further investigations of lung adenocarcinoma molecular pathogenesis.

Cope, L. M., Fackler, M. J., Lopez-Bujanda, Z., Wolff, A. C., Visvanathan, K., Gray, J. W., et al. (2014). Do breast cancer cell lines provide a relevant model of the patient tumor methylome? *PloS One, 9*(8), e105545.

It is well documented that tumor cells undergo dramatic genetic and epigenetic changes during initial establishment as cell lines and in subsequent serial passaging, and that the resultant cell lines may have evolved significantly from the primary tumors from which they were derived. This has potential implications due to their widespread use in drug response experiments and studies of genomic function. One approach to optimizing the design of such cell line studies is to identify and use the cell lines that faithfully recapitulate critical features of primary tumors. To evaluate the epigenetic fidelity of breast cancer cell lines in the context of primary tumors, we performed methylation profiling of 55 well-characterized breast cancer cell lines on the Illumina HumanMethylation27 BeadChip platform, and compared them to publicly available methylation profiles of primary breast tumors. We found that the DNA methylation profiles of breast cancer cell lines largely retain the features that characterize primary tumors, although there are crucial differences as well. We describe these similarities and differences between primary tumors and breast cancer cell lines in detail, and develop a quantitative measure of similarity that is used to score each cell line with respect to how faithfully its methylation profile mirrors that of primary tumors.

Cowley, D., Dunaway, K., Forstein, M., Frosch, E., Han, J., Joseph, R., et al. (2014). Teaching psychiatry residents to work at the interface of mental health and primary care. *Academic Psychiatry, 38*(4), 398-404.

The authors present examples of programs educating psychiatry residents to work in integrated healthcare settings.

Crittenden, M. R., Savage, T., Cottam, B., Baird, J., Rodriguez, P. C., Newell, P., et al. (2014). Expression of arginase i in myeloid cells limits control of residual disease after radiation therapy of tumors in mice. *Radiation Research, 182*(2), 182-190.

An accumulating body of evidence demonstrates that radiation therapy can generate adaptive immune responses that contribute to tumor control. However, in the absence of additional immune therapy, the adaptive immune response is insufficient to prevent tumor recurrence or affect distant disease. It has been shown in multiple models that tumor-infiltrating myeloid cells exhibit alternative activation phenotypes and are able to suppress adaptive immune responses, and recent data suggests that the myeloid response in tumors treated with cytotoxic therapy limits tumor control. We hypothesized that tumor myeloid cells inhibit the adaptive immune response after radiation therapy through expression of the enzyme arginase I. Using a myeloid cell-specific deletion of arginase I in mice, we demonstrate an improved tumor control after radiation therapy. However, tumors still recurred despite the conditional knockdown of arginase I. Since multiple alternative factors may combine to inhibit adaptive immunity, we propose that targeting macrophage differentiation may be a more effective strategy than targeting individual suppressive pathways. © 2014 by Radiation Research Society.

Cunningham, C. L. (2014). Genetic relationship between ethanol-induced conditioned place preference and other ethanol phenotypes in 15 inbred mouse strains. *Behavioral Neuroscience, 128*(4), 430-445.

The genetic relationships between different behaviors used to index the rewarding or reinforcing effects of alcohol are poorly understood. To address this issue, ethanol-induced conditioned place preference (CPP) was tested in a genetically diverse panel of inbred mouse strains, and strain means from this study and other inbred strain studies were used to examine the genetic correlation between CPP and several ethanol-related phenotypes, including activity measures recorded during CPP training and testing. Mice from each strain were exposed to a well-characterized unbiased place conditioning procedure using ethanol doses of 2 or 4 g/kg; an additional group from each strain was exposed to saline alone on all trials. Genotype had a significant effect on CPP, basal locomotor activity, ethanol-stimulated activity, and the effect of repeated ethanol exposure on activity. Correlational analyses showed significant negative genetic

correlations between CPP and sweetened ethanol intake and between CPP and test session activity, as well as a significant positive genetic correlation between CPP and chronic ethanol withdrawal severity. Moreover, there was a trend toward a positive genetic correlation between CPP and ethanol-induced conditioned taste aversion. These genetic correlations suggest overlap in the genetic mechanisms underlying CPP and each of these traits. The patterns of genetic relationships suggest a greater impact of ethanol's aversive effects on drinking and a greater impact of ethanol's rewarding effects on CPP. Overall, these data support the idea that genotype influences ethanol's rewarding effect, a factor that may contribute importantly to addictive vulnerability.

Cunningham, C. L., & Zerizef, C. L. (2014). Effects of combining tactile with visual and spatial cues in conditioned place preference. *Pharmacology, Biochemistry, and Behavior, 124*, 443-450.

Previous research provides little information about variables that determine which elements of contextual cues gain associative control over behavior in the conditioned place preference (CPP) procedure. These studies examined the effect of external visual-spatial cues on CPP when tactile cues served as the conditioned stimuli. DBA/2J mice were trained in the dark (Experiment 1) or light (Experiment 2) using unbiased procedures in which the spatial location of an ethanol-paired tactile cue during training was relevant (two-compartment procedure) or irrelevant (one-compartment procedure). All groups developed CPP, but it was weakest after one-compartment training in the light. In Experiment 3, tactile cues were tested either in the same locations used during training or reversed after two-compartment training in either the dark or light. CPP was unaffected by cue location reversal in the dark, but it was reduced when cue locations changed in the light. Mice in Experiment 4 also received two-compartment training in either the light or dark, but the spatial locations of the drug- and vehicle-paired cues alternated over trials, making external visual-spatial cues irrelevant. In this case, lighting had no effect on CPP. These studies show that cue location does not affect CPP when tactile cue training occurs in the dark. Moreover, they suggest that external visual-spatial cues might enhance CPP when those cues are relevant, but not when an alternating two-compartment procedure is used. The cue reversal effect suggests that relevant external visual-spatial cues acquire associative strength when combined with tactile cues in a two-compartment procedure in the light. Overall, these studies improve our

understanding of how external visual-spatial cues interact with tactile cues during drug-induced conditioning, which could have important implications for studies that use CPP to study the neurobiological bases of drug seeking and drug reward.

Dahdul, W. M., Cui, H., Mabee, P. M., Mungall, C. J., Osumi-Sutherland, D., Walls, R. L., et al. (2014). Nose to tail, roots to shoots: Spatial descriptors for phenotypic diversity in the biological spatial ontology. *Journal of Biomedical Semantics, 5*, 34-1480-5-34. eCollection 2014.

BACKGROUND: Spatial terminology is used in anatomy to indicate precise, relative positions of structures in an organism. While these terms are often standardized within specific fields of biology, they can differ dramatically across taxa. Such differences in usage can impair our ability to unambiguously refer to anatomical position when comparing anatomy or phenotypes across species. We developed the Biological Spatial Ontology (BSPO) to standardize the description of spatial and topological relationships across taxa to enable the discovery of comparable phenotypes. RESULTS: BSPO currently contains 146 classes and 58 relations representing anatomical axes, gradients, regions, planes, sides, and surfaces. These concepts can be used at multiple biological scales and in a diversity of taxa, including plants, animals and fungi. The BSPO is used to provide a source of anatomical location descriptors for logically defining anatomical entity classes in anatomy ontologies. Spatial reasoning is further enhanced in anatomy ontologies by integrating spatial relations such as dorsal_to into class descriptions (e.g., 'dorsolateral placode' dorsal_to some 'epibranchial placode'). CONCLUSIONS: The BSPO is currently used by projects that require standardized anatomical descriptors for phenotype annotation and ontology integration across a diversity of taxa. Anatomical location classes are also useful for describing phenotypic differences, such as morphological variation in position of structures resulting from evolution within and across species.

Davidson, B. P., Belcik, J. T., Mott, B. H., Landry, G., & Lindner, J. R. (2014). Quantification of residual limb skeletal muscle perfusion with contrast-enhanced ultrasound during application of a focal junctional tourniquet. *Journal of Vascular Surgery,*

OBJECTIVE: Focal junctional tourniquets (JTs) have been developed to control hemorrhage from proximal limb injuries. These devices may permit greater collateral perfusion than circumferential

tourniquets. We hypothesized that JTs eliminate large-vessel pulse pressure yet allow a small amount of residual limb perfusion that could be useful for maintaining tissue viability. METHODS: Ten healthy control subjects were studied. Transthoracic echocardiography, Doppler ultrasound of the femoral artery (FA) and posterior tibial artery, and contrast-enhanced ultrasound (CEU) perfusion imaging of the anterior thigh extensor and calf plantar flexor muscles were performed at baseline and during application of a JT over the common FA. Intramuscular arterial pulsatility index was also measured from CEU intensity variation during the cardiac cycle. RESULTS: FA flow was eliminated by JTs in all subjects; posterior tibial flow was eliminated in all but one. Perfusion measured in the thigh and calf muscles was similar at baseline (0.33 +/- 0.29 vs 0.29 +/- 0.22 mL/min/g). Application of the JT resulted in a reduction of perfusion ($P < .05$) that was similar for the thigh and calf (0.08 +/- 0.07 and 0.10 +/- 0.03 mL/min/g). On CEU, microvascular flux rate was reduced by approximately 55%, and functional microvascular blood volume was reduced by approximately 35%. Arterial pulsatility index was reduced by approximately 90% in the calf. JT inflation did not alter left ventricle dimensions, fractional shortening, cardiac output, or arterial elastance as a measure of total systolic load. CONCLUSIONS: Application of a JT eliminates conduit arterial pulse and markedly reduces intramuscular pulse pressure, but thigh and calf skeletal muscle perfusion is maintained at 25% to 35% of basal levels. These data suggest that JTs that are used to control limb hemorrhage allow residual tissue perfusion even when pulse pressure is absent.

DeConde, A. S., Bodner, T. E., Mace, J. C., & Smith, T. L. (2014). Response shift in quality of life after endoscopic sinus surgery for chronic rhinosinusitis. *JAMA Otolaryngology-- Head & Neck Surgery, 140*(8), 712-719.

IMPORTANCE: Patient-reported measures are designed to detect a true change in outcome, but they are also subject to change from biases inherent to self-reporting: changing internal standards, changing priorities, and changing interpretations of a given instrument. These biases are collectively known as "response shifts" and can obscure true change after medical interventions. OBJECTIVE: To determine the presence of response shifts in patients with chronic rhinosinusitis (CRS) after endoscopic sinus surgery. DESIGN, SETTING, AND PARTICIPANTS: Multisite, prospective, observational cohort study conducted at academic tertiary care centers

between February 2011 and May 2013. Study participants comprised a population-based sample of 514 adults (age >/=18 years) with CRS, who elected surgical intervention for continuing medically refractory symptoms. INTERVENTION: Endoscopic sinus surgery. MAIN OUTCOMES AND MEASURES: Preoperative and postoperative data from the 22-item Sinonasal Outcome Test (SNOT-22) survey instrument was characterized using exploratory factor analysis. Subsequent longitudinal structural equation models were estimated to test structure, potential response shifts, and true change in the SNOT-22 scores. RESULTS: A total of 339 participants (66.0%) provided survey evaluations at baseline and 6-month follow-up. Factor analysis of the SNOT-22 revealed 5 correlated, yet distinguishable, underlying factors. Endoscopic sinus surgery had a differential impact across these factors, with the largest effect size in rhinologic symptoms (mean [SD] SNOT-22 scores before and after surgery, 13.18 [5.11] and 7.37 [5.48], respectively; d = -1.13 [P < .001]) and extranasal rhinologic symptoms (8.31 [3.46] and 4.83 [3.68], respectively; d = -1.00 [P < .05]) (d is an effect size measure defined as the difference in means divided by the presurgery SD). Endoscopic sinus surgery had a smaller, yet significant, effect size on the remaining 3 factors: ear/facial symptoms (7.32 [4.6]) and 3.90 [4.07], respectively; d = -0.74 [P < .001]), psychological dysfunction (11.90 [7.21] and 6.50 [6.69], respectively; d = -0.75 [P < .05]), and sleep dysfunction (10.12 [5.59] and 5.88 [5.37], respectively; d = -0.76 [P < .001]). Participants were found to undergo recalibration, reprioritization, and reconceptualization of symptoms after intervention; however, the magnitude of these response shifts was small and not clinically significant. CONCLUSIONS AND RELEVANCE: The SNOT-22 measures 5 distinct factors, not a single construct. Reporting of individual subscale scores may improve sensitivity of this instrument in future studies. Participants undergoing endoscopic sinus surgery experience only clinically insignificant response shifts, validating assessment of change through use of presurgery and postsurgery SNOT-22 responses. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT01332136.

Deconde, A. S., Mace, J. C., & Smith, T. L. (2014). The impact of comorbid gastroesophageal reflux disease on endoscopic sinus surgery quality-of-life outcomes. *International Forum of Allergy and Rhinology, 4*(8), 663-669.

Background: Chronic rhinosinusitis (CRS) and gastroesophageal reflux disease (GERD) are

common entities that overlap in patient demographics. The pathophysiologic role of GERD has yet to be elucidated, but it is postulated that extraesophageal reflux may contribute to worsening symptoms of CRS. This study seeks to investigate whether patients with CRS with and without a history of GERD experience comparable quality-of-life (QOL) improvement after endoscopic sinus surgery (ESS). Methods: An adult cohort (n = 229) with medically refractory CRS was prospectively assessed following ESS using 3 disease-specific QOL constructs. A patient subset with a history of comorbid GERD was retrospectively identified (n = 72) and preoperative and postoperative QOL were compared to patients without GERD (n = 157). Results: Patients with comorbid GERD and CRS were comparable across all baseline patient characteristics (p > 0.050) with the exception of patients with a history of GERD; those patients were less likely to have undergone allergy testing (p 0.050). Both groups experienced significant QOL improvement across all QOL constructs (p ≤ 0.021), and no difference was detected in the magnitude of that improvement between patients with and without a history of GERD (p > 0.050). Similarly, patients on active medical therapy for GERD (n = 49) had QOL gaihttp://www.nytimes.com/2012/06/19/us/asians-surpass-hispanics-as-biggest-immigrant-wave.html?_r=0ns comparable to patients not reporting GERD medical therapy (p > 0.050). Conclusion: Patients electing ESS for CRS with and without comorbid GERD have comparable baseline characteristics and QOL outcomes following surgery. © 2014 ARS-AAOA, LLC.

DeHaan, A. M., Adams, J. R., DeHart, M. L., & Huff, T. W. (2014). Patient-specific versus conventional instrumentation for total knee arthroplasty: Peri-operative and cost differences. *The Journal of Arthroplasty,*

The role of patient-specific instrumentation in total knee arthroplasty (TKA) is yet to be clearly defined. Current evidence evaluating peri-operative and cost differences against conventional TKA is unclear. We reviewed 356 TKAs between July 2008 and April 2013; 306 TKAs used patient-specific instrumentation while 50 had conventional instrumentation. The patient-specific instrumentation cohort averaged 20.4 min less surgical time (P < 0.01) and had a 42% decrease in operating room turnover time (P = 0.022). At our institution, the money saved through increased operating room efficiency offset the cost of the custom cutting blocks and pre-operative advanced imaging. Routine use of patient-specific TKA can be performed with less surgical time,

no increase in peri-operative morbidity, and at no increased cost when compared to conventional TKA.

Del Prete, G. Q., Park, H., Fennessey, C. M., Reid, C., Lipkey, L., Newman, L., et al. (2014). Molecularly tagged simian immunodeficiency virus SIVmac239 synthetic swarm for tracking independent infection events. *Journal of Virology, 88*(14), 8077-8090.

Following mucosal human immunodeficiency virus type 1 transmission, systemic infection is established by one or only a few viral variants. Modeling single-variant, mucosal transmission in nonhuman primates using limiting-dose inoculations with a diverse simian immunodeficiency virus isolate stock may increase variability between animals since individual variants within the stock may have substantial functional differences. To decrease variability between animals while retaining the ability to enumerate transmitted/founder variants by sequence analysis, we modified the SIVmac239 clone to generate 10 unique clones that differ by two or three synonymous mutations (molecular tags). Transfection- and infection-derived virus stocks containing all 10 variants showed limited phenotypic differences in 9 of the 10 clones. Twenty-nine rhesus macaques were challenged intrarectally or intravenously with either a single dose or repeated, limiting doses of either stock. The proportion of each variant within each inoculum and in plasma from infected animals was determined by using a novel real-time single-genome amplification assay. Each animal was infected with one to five variants, the number correlating with the dose. Longitudinal sequence analysis revealed that the molecular tags are highly stable with no reversion to the parental sequence detected in >2 years of follow-up. Overall, the viral stocks are functional and mucosally transmissible and the number of variants is conveniently discernible by sequence analysis of a small amplicon. This approach should be useful for tracking individual infection events in preclinical vaccine evaluations, long-term viral reservoir establishment/clearance research, and transmission/early-event studies. Importance: Human immunodeficiency virus type 1 transmission is established by one or only a few viral variants. Modeling of limited variant transmission in nonhuman primates with a diverse simian immunodeficiency virus isolate stock may increase the variability between animals because of functional differences in the individual variants within the stock. To decrease such variability while retaining the ability to distinguish and enumerate transmitted/founder variants by sequence

analysis, we generated a viral stock with 10 sequence-identifiable but otherwise genetically identical variants. This virus was characterized in vitro and in vivo and shown to allow discrimination of distinct transmission events. This approach provides a novel nonhuman primate challenge system for the study of viral transmission, evaluation of vaccines and other prevention approaches, and characterization of viral reservoirs and strategies to target them.

Deveney, K. E. (2014). Transition from residency to practice: Life does get better! *JAMA Surgery,*

DeVoe, J. E., Tillotson, C. J., Angier, H., & Wallace, L. S. (2014). Predictors of children's health insurance coverage discontinuity in 1998 versus 2009: Parental coverage continuity plays a major role. *Maternal and Child Health Journal,*

To identify predictors of coverage continuity for United States children and assess how they have changed in the first 12 years since implementation of the Children's Health Insurance Program in 1997. Using data from the nationally-representative Medical Expenditure Panel Survey, we used logistic regression to identify predictors of discontinuity in 1998 and 2009 and compared differences between the 2 years. Having parents without continuous coverage was the greatest predictor of a child's coverage gap in both 1998 and 2009. Compared to children with at least one parent continuously covered, children whose parents did not have continuous coverage had a significantly higher relative risk (RR) of a coverage gap [RR 17.96, 95 % confidence interval (CI) 14.48-22.29 in 1998; RR 12.88, 95 % CI 10.41-15.93 in 2009]. In adjusted models, parental continuous coverage was the only significant predictor of discontinuous coverage for children (with one exception in 2009). The magnitude of the pattern was higher for privately-insured children [adjusted relative risk (aRR) 29.17, 95 % CI 20.99-40.53 in 1998; aRR 25.54, 95 % CI 19.41-33.61 in 2009] than publicly-insured children (aRR 5.72, 95 % CI 4.06-8.06 in 1998; aRR 4.53, 95 % CI 3.40-6.04 in 2009). Parental coverage continuity has a major influence on children's coverage continuity; this association remained even after public health insurance expansions for children. The Affordable Care Act will increase coverage for many adults; however, 'churning' on and off programs due to income fluctuations could result in coverage discontinuities for parents. If parental coverage instability persists, these discontinuities may continue to have a negative impact on children's coverage stability as well.

DeVon, H. A., Rosenfeld, A., Steffen, A. D., & Daya, M. (2014). Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *Journal of the American Heart Association, 3*(2)

Background: Clinical symptoms are part of the risk stratification approaches used in the emergency department (ED) to evaluate patients with suspected acute coronary syndromes (ACS). The objective of this study was to determine the sensitivity, specificity, and predictive value of 13 symptoms for a discharge diagnosis of ACS in women and men. Methods and Results: The sample included 736 patients admitted to 4 EDs with symptoms suggestive of ACS. Symptoms were assessed with the 13-item validated ACS Symptom Checklist. Mixed-effects logistic regression models were used to estimate sensitivity, specificity, and predictive value of each symptom for a diagnosis of ACS, adjusting for age, obesity, diabetes, and functional status. Patients were predominantly male (63%) and Caucasian (70.5%), with a mean age of 59.7±14.2 years. Chest pressure, chest discomfort, and chest pain demonstrated the highest sensitivity for ACS in both women (66%, 66%, and 67%) and men (63%, 69%, and 72%). Six symptoms were specific for a non-ACS diagnosis in both women and men. The predictive value of shoulder (odds ratio [OR]=2.53; 95% CI=1.29 to 4.96) and arm pain (OR 2.15; 95% CI=1.10 to 4.20) in women was nearly twice that of men (OR=1.11; 95% CI=0.67 to 1.85 and OR=1.21; 95% CI=0.74 to 1.99). Shortness of breath (OR=0.49; 95% CI=0.30 to 0.79) predicted a non-ACS diagnosis in men. Conclusions: There were more similarities than differences in symptom predictors of ACS for women and men. © 2014 The Authors.

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., et al. (2014). Report of the NIH task force on research standards for chronic low back pain. *Pain Medicine (Malden, Mass.), 15*(8), 1249-1267.

OBJECTIVE: Despite rapidly increasing intervention, functional disability due to chronic low back pain (cLBP) has increased in recent decades. We often cannot identify mechanisms to explain the major negative impact cLBP has on patients' lives. Such cLBP is often termed non-specific, and may be due to multiple biologic and behavioral etiologies. Researchers use varied inclusion criteria, definitions, baseline assessments, and outcome measures, which impede comparisons and consensus. DESIGN: Expert panel and preliminary evaluation of key recommendations.

METHODS: The NIH Pain Consortium charged a Research Task Force (RTF) to draft standards for research on cLBP. The resulting multidisciplinary panel developed a 3-stage process, each with a 2-day meeting. RESULTS: The panel recommended using 2 questions to define cLBP; classifying cLBP by its impact (defined by pain intensity, pain interference, and physical function); use of a minimal data set to describe research subjects (drawing heavily on the PROMIS methodology); reporting "responder analyses" in addition to mean outcome scores; and suggestions for future research and dissemination. The Pain Consortium has approved the recommendations, which investigators should incorporate into NIH grant proposals. CONCLUSION: The RTF believes these recommendations will advance the field, help to resolve controversies, and facilitate future research addressing the genomic, neurologic, and other mechanistic substrates of chronic low back pain. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes. We expect the RTF recommendations will become a dynamic document, and undergo continual improvement. PERSPECTIVE: A task force was convened by the NIH Pain Consortium with the goal of developing research standards for chronic low back pain. The results included recommendations for definitions, a minimum dataset, reporting outcomes, and future research. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes.

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., et al. (2014). Report of the national institutes of health task force on research standards for chronic low back pain. *Journal of Manipulative and Physiological Therapeutics,*

OBJECTIVES: Despite rapidly increasing intervention, functional disability due to chronic low back pain (cLBP) has increased in recent decades. We often cannot identify mechanisms to explain the major negative impact cLBP has on patients' lives. Such cLBP is often termed nonspecific and may be due to multiple biologic and behavioral etiologies. Researchers use varied inclusion criteria, definitions, baseline assessments, and outcome measures, which impede comparisons and consensus. The purpose of this article is to disseminate the report of the National Institutes of Health (NIH) task force on research standards for cLBP. METHODS: The NIH Pain Consortium charged a research task force (RTF) to draft standards for research on cLBP. The resulting multidisciplinary panel developed a 3-stage process, each with a 2-day meeting. RESULTS: The

panel recommended using 2 questions to define cLBP; classifying cLBP by its impact (defined by pain intensity, pain interference, and physical function); use of a minimal data set to describe research subjects (drawing heavily on the Patient Reported Outcomes Measurement Information System methodology); reporting "responder analyses" in addition to mean outcome scores; and suggestions for future research and dissemination. The Pain Consortium has approved these recommendations, which investigators should incorporate into NIH grant proposals. CONCLUSIONS: The RTF believes that these recommendations will advance the field, help to resolve controversies, and facilitate future research addressing the genomic, neurologic, and other mechanistic substrates of cLBP. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes. We expect the RTF recommendations will become a dynamic document and undergo continual improvement.

Dieperink, E., Fuller, B., Isenhart, C., Mcmaken, K., Lenox, R., Pocha, C., et al. (2014). Efficacy of motivational enhancement therapy on alcohol use disorders in patients with chronic hepatitis C: A randomized controlled trial. *Addiction,*

Aims: To determine the efficacy of motivational enhancement therapy (MET) on alcohol use in patients with the hepatitis C virus (HCV) and an alcohol use disorder (AUD). Design: Randomized, single-blind, controlled trial comparing MET to a control education condition with 6-month follow-up. Setting: Patients were recruited from hepatitis clinics at the Minneapolis, Minnesota and Portland, Oregon Veterans Affairs Health Care Systems, USA. Participants and Intervention: Patients with HCV, an AUD and continued alcohol use (n=139) were randomized to receive either MET (n=70) or a control education condition (n=69) over 3 months. Measurements: Data were self-reported percentage of days abstinent from alcohol and number of standard alcohol drinks per week 6 months after randomization. Findings: At baseline, subjects in MET had 34.98% days abstinent, which increased to 73.15% at 6 months compared to 34.63 and 59.49% for the control condition. Multi-level models examined changes in alcohol consumption between MET and control groups. Results showed a significant increase in percentage of days abstinent overall ($F(1120.4)=28.04$, $P<0.001$) and a significant group×time effect ($F(1119.9)=5.23$, $P=0.024$) with the MET group showing a greater increase in percentage of days abstinent at 6 months compared with the education control condition. There were no significant differences between

groups for drinks per week. The effect size of the MET intervention was moderate (0.45) for percentage of days abstinent. Conclusion: Motivational enhancement therapy (MET) appears to increase the percentage of days abstinent in patients with chronic hepatitis C, alcohol use disorders and ongoing alcohol use. © 2014 Society for the Study of Addiction September 2014.

Dikici, E., Prud'hommeaux, E., Roark, B., & Saraçlar, M. (2013). Investigation of MT-based ASR confusion models for semi-supervised discriminative language modeling. *14th Annual Conference of the International Speech Communication Association, INTERSPEECH 2013,* Lyon. pp. 1218-1222.

Semi-supervised discriminative language modeling uses simulated N-best lists instead of real ASR outputs as its training examples. In this study we apply two techniques in which artificial examples are generated using a WFST and an MT system trained on pairs of reference text and ASR output. We compare the performance of these techniques with the structured prediction and ranking variants of the WER-sensitive perceptron algorithm, and contrast with the supervised case where real ASR outputs are given as input. Choosing Turkish statistical morphs as n-gram features, we analyze the similarities between the hypotheses of these three setups and the number of utilized features. We show that the MT-based system yields the lowest WER, not only because the examples generated by this technique are more effective, but also because the ranking perceptron generalizes better with this setup. When trained on a combination of artificial WFST and MT data, the structured perceptron performs as well on an unseen test set as it does when trained on real ASR output. Copyright © 2013 ISCA.

Dorrell, C., Tarlow, B., Wang, Y., Canaday, P. S., Haft, A., Schug, J., et al. (2014). The organoid-initiating cells in mouse pancreas and liver are phenotypically and functionally similar. *Stem Cell Research, 13*(2), 275-283.

Pancreatic Lgr5 expression has been associated with organoid-forming epithelial progenitor populations but the identity of the organoid-initiating epithelial cell subpopulation has remained elusive. Injury causes the emergence of an Lgr5+ organoid-forming epithelial progenitor population in the adult mouse liver and pancreas. Here, we define the origin of organoid-initiating cells from mouse pancreas and liver prior to Lgr5 activation. This clonogenic population was

defined as MIC1-1C3+/CD133+/CD26- in both tissues and the frequency of organoid initiation within this population was approximately 5% in each case. The transcriptomes of these populations overlapped extensively and showed enrichment of epithelial progenitor-associated regulatory genes such as Sox9 and FoxJ1. Surprisingly, pancreatic organoid cells also had the capacity to generate hepatocyte-like cells upon transplantation to Fah-/- mice, indicating a differentiation capacity similar to hepatic organoids. Although spontaneous endocrine differentiation of pancreatic progenitors was not observed in culture, adenoviral delivery of fate-specifying factors Pdx1, Neurog3 and MafA induced insulin expression without glucagon or somatostatin. Pancreatic organoid cultures therefore preserve many key attributes of progenitor cells while allowing unlimited expansion, facilitating the study of fate determination.

Duke, D. C., & Harris, M. A. (2014). Executive function, adherence, and glycemic control in adolescents with type 1 diabetes: A literature review. *Current Diabetes Reports, 14*(10), 532-014-0532-y.

The aim of the present review was to examine and report findings from published research to date that has examined associations between executive function (EF), adherence, and glycemic control in youth with type 1 diabetes. A review of the published research is presented with the objectives of reporting the following: (1) the associations between EF and adherence, (2) the associations between EF and glycemic control, (3) proposed methodological considerations needed to advance related research, (4) recommendations for future research, and (5) clinical recommendations. The major conclusions of this review support the presence of an association between EF, adherence, and glycemic control. Additional prospective and controlled studies are necessary to fully understand the impact of EF on the ability of youth to independently manage type 1 diabetes.

Durr, K. L., Chen, L., Stein, R. A., De Zorzi, R., Folea, I. M., Walz, T., et al. (2014). Structure and dynamics of AMPA receptor GluA2 in resting, pre-open, and desensitized states. *Cell, 158*(4), 778-792.

Ionotropic glutamate receptors (iGluRs) mediate the majority of fast excitatory signaling in the nervous system. Despite the profound importance of iGluRs to neurotransmission, little is known

about the structures and dynamics of intact receptors in distinct functional states. Here, we elucidate the structures of the intact GluA2 AMPA receptor in an apo resting/closed state, in an activated/pre-open state bound with partial agonists and a positive allosteric modulator, and in a desensitized/closed state in complex with fluorowilliardiine. To probe the conformational properties of these states, we carried out double electron-electron resonance experiments on cysteine mutants and cryoelectron microscopy studies. We show how agonist binding modulates the conformation of the ligand-binding domain "layer" of the intact receptors and how, upon desensitization, the receptor undergoes large conformational rearrangements of the amino-terminal and ligand-binding domains. We define mechanistic principles by which to understand antagonism, activation, and desensitization in AMPA iGluRs.

Duvall, S. W., Erickson, S. J., MacLean, P., & Lowe, J. R. (2014). Perinatal medical variables predict executive function within a sample of preschoolers born very low birth weight. *Journal of Child Neurology,*

The goal was to identify perinatal predictors of early executive dysfunction in preschoolers born very low birth weight. Fifty-seven preschoolers completed 3 executive function tasks: Dimensional Change Card Sort-Separated (inhibition, working memory, and cognitive flexibility), Bear Dragon (inhibition and working memory), and Gift Delay Open (inhibition). Relationships between executive function and perinatal medical severity factors (gestational age, days on ventilation, size for gestational age, maternal steroids, and number of surgeries) and chronological age were investigated by multiple linear regression and logistic regression. Different perinatal medical severity factors were predictive of executive function tasks, with gestational age predicting Bear Dragon and Gift Open; and number of surgeries and maternal steroids predicting performance on Dimensional Change Card Sort-Separated. By understanding the relationship between perinatal medical severity factors and preschool executive outcomes, we can identify children at highest risk for future executive dysfunction, thereby focusing targeted early intervention services.

E-Andjafono, D. O. L., Makila-Mabe, G. B., Ayanne, M. -. S. S., Kikandau, J. K., Mashukano, N., Kazembe, T. K., et al. (2014). Persistence epidemics konzo to kahemba, democratic republic of

congo: Phenomenological aspects and socio-economic. [Persistance des épidémies de konzo à kahemba, république démocratique du congo: Aspects phénoménologiques et socio-économiques] *Pan African Medical Journal, 18*

Edelman, A., Micks, E., Gallo, M. F., Jensen, J. T., & Grimes, D. A. (2014). Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *The Cochrane Database of Systematic Reviews, 7*, CD004695.

BACKGROUND: The avoidance of menstruation through continuous or extended (greater than 28 days) administration of combination hormonal contraceptives (CHCs) has gained legitimacy through its use in treating endometriosis, dysmenorrhea, and menstruation-associated symptoms. Avoidance of menstruation through extended or continuous use of CHCs for reasons of personal preference may have additional advantages to women, including improved compliance, greater satisfaction, fewer menstrual symptoms, and less menstruation-related absenteeism from work or school. OBJECTIVES: To determine the differences between continuous or extended-cycle CHCs (pills, patch, ring) in regimens of greater than 28 days of active hormone compared with traditional cyclic dosing (21 days of active hormone and 7 days of placebo, or 24 days of active hormones and 4 days of placebo). Our hypothesis was that continuous or extended-cycle CHCs have equivalent efficacy and safety but improved bleeding profiles, amenorrhea rates, adherence, continuation, participant satisfaction, and menstrual symptoms compared with standard cyclic CHCs. SEARCH METHODS: We searched computerized databases (Cochrane Central Register of Controlled Trials, PUBMED, EMBASE, POPLINE, LILACS) for trials using continuous or extended CHCs (oral contraceptives, contraceptive ring and patch) during the years 1966 to 2013. We also searched the references in review articles and publications identified for inclusion in the protocol. Investigators were contacted regarding additional references. SELECTION CRITERIA: All randomized controlled trials in any language comparing continuous or extended-cycle (greater than 28 days of active hormones) versus traditional cyclic administration (21 days of active hormones and 7 days of placebo, or 24 days of active hormones and 4 days of placebo) of CHCs for contraception. DATA COLLECTION AND ANALYSIS: Titles and abstracts identified from the literature searches were assessed for potential inclusion. Data were extracted onto data collection forms and then entered into RevMan 5. Peto odds ratios with 95% confidence

intervals were calculated for all outcomes for dichotomous outcomes. Weighted mean difference was calculated for continuous outcomes. The trials were critically appraised by examining the following factors: study design, blinding, randomization method, group allocation concealment, exclusions after randomization, loss to follow-up, and early discontinuation. Because the included trials did not have a standard treatment (type of CHC formulation, route of delivery, or time length for continuous dosing), we could not aggregate data into meta-analysis. MAIN RESULTS: Twelve randomized controlled trials met our inclusion criteria. Study findings were similar between 28-day and extended or continuous regimens in regard to contraceptive efficacy (i.e., pregnancy rates) and safety profiles. When compliance was reported, no difference between 28-day and extended or continuous cycles was found. Participants reported high satisfaction with both dosing regimens, but this was not an outcome universally studied. Overall discontinuation and discontinuation for bleeding problems were not uniformly higher in either group. The studies that reported menstrual symptoms found that the extended or continuous group fared better in terms of headaches, genital irritation, tiredness, bloating, and menstrual pain. Eleven out of the twelve studies found that bleeding patterns were either equivalent between groups or improved with extended or continuous cycles over time. Endometrial lining assessments by ultrasound and/or endometrial biopsy were done in some participants and were all normal after cyclic or extended CHC use. AUTHORS' CONCLUSIONS: The 2014 update yielded four additional trials but unchanged conclusions. Evidence from existing randomized control trials comparing continuous or extended-cycle CHCs (greater than 28 days of active combined hormones) to traditional cyclic dosing (21 days of active hormone and 7 days of placebo, or 24 days of active hormone and 4 days of placebo) is of good quality. However, the variations in type of hormones and time length for extended-cycle dosing make a formal meta-analysis impossible. Future studies should choose a previously described type of CHC and dosing regimen. More attention needs to be directed towards participant satisfaction, continuation, and menstruation-associated symptoms.

Edelman, A. B., Cherala, G., Munar, M. Y., McInnis, M., Stanczyk, F. Z., & Jensen, J. T. (2014). Correcting oral contraceptive pharmacokinetic alterations due to obesity: A randomized controlled trial. *Contraception,*

OBJECTIVE: To determine if increasing the hormone dose or eliminating the hormone-free

interval improves key pharmacokinetic (PK) alterations caused by obesity during oral contraceptive (OC) use. STUDY DESIGN: Obese [body mass index (BMI)>/=30 kg/m2], ovulatory, otherwise healthy, women received an OC containing 20 mcg ethinyl estradiol (EE)/100 mcg levonorgestrel (LNG) dosed cyclically (21 days active pills with 7-day placebo week) for two cycles and then were randomized for two additional cycles to the following: continuous cycling (CC, a dose neutral arm using the same OC with no hormone-free interval) or increased dose (ID, a dose escalation arm using an OC containing 30 mcg EE/150 mcg LNG cyclically). During Cycles 2, 3 and 4, outpatient visits were performed to assess maximum serum concentration (Cmax), area under the curve (AUC0-infinity) and time to steady state as well as pharmacodynamics. These key PK parameters were calculated and compared within groups between baseline and treatment cycles. RESULTS: A total of 31 women enrolled and completed the study (CC group, n=16; ID group, n=15). Demographics were similar between groups [mean BMI: CC, 38 kg/m2 (S.D. 5.1); ID, 41 kg/m2 (S.D. 7.6)]. At baseline, the key LNG PK parameters were no different between groups; average time to reach steady state was 12 days in both groups; Cmax were CC: 3.82+/-1.28 ng/mL and ID: 3.13+/-0.87 ng/mL; and AUC0-infinity were CC: 267+/-115 h ng/mL and ID: 199+/-75 h ng/mL. Following randomization, the CC group maintained steady-state serum levels whereas the ID group had a significantly higher Cmax (p<.001) but again required 12 days to achieve steady state. However, AUC was not significantly different between CC (412+/-255 h ng/mL) and ID (283+/-130 h ng/mL). Forty-five percent (14/31) of the study population had evidence of an active follicle-like structure prior to randomization and afterwards this decreased to 9% (3/31). CONCLUSION: Both increasing the OC dose and continuous dosing appear to counteract the impact of obesity on key OC PK parameters. IMPLICATIONS: Obesity adversely affects the pharmacokinetics of very low dose OC pills. Although the impact of these changes on OC efficacy is still under debate, PK parameters can be normalized in obese users by continuous dosing or increasing to a low-dose pill.

El Youssef, J., Castle, J. R., Bakhtiani, P. A., Haidar, A., Branigan, D. L., Breen, M., et al. (2014). Quantification of the glycemic response to microdoses of subcutaneous glucagon at varying insulin levels. *Diabetes Care,*

OBJECTIVE: Glucagon delivery in closed-loop control of type 1 diabetes is effective in minimizing

hypoglycemia. However, high insulin concentration lowers the hyperglycemic effect of glucagon, and small doses of glucagon in this setting are ineffective. There are no studies clearly defining the relationship between insulin levels, subcutaneous glucagon, and blood glucose. RESEARCH DESIGN AND METHODS: Using a euglycemic clamp technique in 11 subjects with type 1 diabetes, we examined endogenous glucose production (EGP) of glucagon (25, 75, 125, and 175 mug) at three insulin infusion rates (0.016, 0.032, and 0.05 units/kg/h) in a randomized, crossover study. Infused 6,6-dideuterated glucose was measured every 10 min, and EGP was determined using a validated glucoregulatory model. Area under the curve (AUC) for glucose production was the primary outcome, estimated over 60 min. RESULTS: At low insulin levels, EGP rose proportionately with glucagon dose, from 5 +/- 68 to 112 +/- 152 mg/kg (P = 0.038 linear trend), whereas at high levels, there was no increase in glucose output (19 +/- 53 to 26 +/- 38 mg/kg, P = NS). Peak glucagon serum levels and AUC correlated well with dose (r2 = 0.63, P < 0.001), as did insulin levels with insulin infusion rates (r2 = 0.59, P < 0.001). CONCLUSIONS: EGP increases steeply with glucagon doses between 25 and 175 mug at lower insulin infusion rates. However, high insulin infusion rates prevent these doses of glucagon from significantly increasing glucose output and may reduce glucagon effectiveness in preventing hypoglycemia when used in the artificial pancreas.

Faridi, A., Yeh, S., Suhler, E. B., Smith, J. R., & Flaxel, C. J. (2014). Retinal detachment associated with ocular toxoplasmosis. *Retina (Philadelphia, Pa.),*

PURPOSE:: To assess the frequency of retinal detachment (RD) and associated clinical features in ocular toxoplasmosis. METHODS:: A review of the medical records of patients diagnosed with ocular toxoplasmosis and follow-up of 6 months or more was conducted. All patients were seen at the Casey Eye Institute at the Oregon Health & Science University over a 9-year period (2003-2012). Demographic data, presence of RD and/or vitritis, and treatments were reviewed. Main outcome measures were the rate of RD in ocular toxoplasmosis, degree of vision loss, and final anatomical status of the retina. Disease- and treatment-related factors associated with poor visual outcome were also analyzed. RESULTS:: Thirty-five eyes of 28 patients with ocular toxoplasmosis and sufficient follow-up were studied. Median age of patients was 40 years (range, 7-93 years). Median follow-up time was 22.5 months (range, 6-96 months). Four of thirty-five

eyes (11.4%) developed RD with a frequency of 0.06 RD events per patient-year of follow-up in this sample in a single center. Of four patients with RD, three underwent pars plana vitrectomy and one underwent laser retinopexy. Two of the 4 patients had recurrent RD requiring scleral buckle. At final follow-up, all patients who underwent surgical repair had attached retinas; however, 3 of 4 patients had severe vision loss (20/200 or worse). CONCLUSION:: Retinal detachment occurred in 11% of eyes in this study that led to severe vision loss despite successful RD repair.

Fazio, S., & Tavori, H. (2014). Peeking into a cool future: Genome editing to delete PCSK9 and control hypercholesterolemia in a single shot. *Circulation Research, 115*(5), 472-474.

Fender, E. A., Henrikson, C. A., & Tereshchenko, L. (2014). Racial differences in sudden cardiac death. *Journal of Electrocardiology,*

There is an increased risk of sudden cardiac death (SCD) and sudden cardiac arrest (SCA), in African Americans, the basis of which is likely multifactorial. African Americans have higher rates of traditional cardiac risk factors including hypertension, left ventricular hypertrophy, diabetes, coronary heart disease, and heart failure. There are also significant disparities in health care delivery. While these factors undoubtedly affect health outcomes, there is also growing evidence that genetics may have a significant impact as well. In this paper, we discuss data and hypotheses in support of both sides of the controversy around racial differences in SCD/SCA.

Flatley, E., Chen, A. I., Zhao, X., Jaffe, E. S., Dunlap, J. B., Pittaluga, S., et al. (2014). Aberrations of MYC are a common event in B-cell prolymphocytic leukemia. *American Journal of Clinical Pathology, 142*(3), 347-354.

OBJECTIVES: B-cell prolymphocytic leukemia (B-PLL) remains a controversial entity, and its molecular pathogenesis is largely unknown. Patients are older, typically having marked lymphocytosis and splenomegaly in the absence of lymphadenopathy. It is defined as a mature B-cell leukemia with more than 55% circulating prolymphocytes. Leukemic mantle cell lymphoma and chronic lymphocytic leukemia in prolymphocytic transformation must be excluded. METHODS: Case archives were retrospectively reviewed for B-PLL in patients without a previous diagnosis of chronic lymphocytic leukemia or other B-cell neoplasm. RESULTS: We identified six

cases of B-PLL with available cytogenetic data, five of which showed evidence of aberrations in MYC. Three cases showed additional signals for the MYC gene by fluorescence in situ hybridization (FISH), and two cases demonstrated t(8;14)MYC/IGH by karyotyping or FISH. High levels of MYC protein expression were detected in all cases tested with MYC aberrations. CONCLUSIONS: These results suggest that deregulation of MYC plays an important role in the pathogenesis of B-PLL and expands the spectrum of B-cell neoplasms associated with aberrations of MYC.

Fleseriu, M., & Cuevas-Ramos, D. (2014). Treatment of cushing's disease: A mechanistic update. *The Journal of Endocrinology,*

Cushing's disease (CD) is characterized by an adrenocorticotropin (ACTH)-producing anterior corticotroph pituitary adenoma. Hypothalamus-pituitary-adrenal (HPA) axis physiology is disrupted, ACTH secretion increases, which in turn stimulates adrenocortical steroidogenesis and cortisol production. Medical treatment plays an important role for patients with persistent disease after surgery, for those in whom surgery is not feasible, or while awaiting effects of radiation. Multiple drugs, with different mechanisms of action and variable efficacy and tolerability to control the deleterious effects of chronic glucocorticoid excess, are available. The molecular basis and clinical data for centrally acting drugs, adrenal steroidogenesis inhibitors, and glucocorticoid receptor antagonists are reviewed, as are potential novel molecules and future possible targets for CD treatment. Although progress has been made in the understanding of specific corticotroph adenoma receptor physiology and recent clinical studies have shown improved effects with a combined medical therapy approach, there is a clear need for a more efficacious and better-tolerated medical therapy for CD patients. A better understanding of the molecular mechanisms in CD and of HPA axis physiology should advance the development of new drugs in the future.

Fling, B. W., Nutt, J. G., & Horak, F. B. (2014). Reply: Does dominant pedunculopontine nucleus exist? *Brain : A Journal of Neurology,*

Fontes, R. B. V., Selden, N. R., & Byrne, R. W. (2014). Fostering and assessing professionalism and communication skills in neurosurgical education. *Journal of Surgical Education,*

Introduction: Incorporation of the 6 ACGME core competencies into surgical training has proven a

considerable challenge particularly for the two primarily behavioral competencies, professionalism and interpersonal and communication skills. We report on experience with two specific interventions to foster the teaching and continuous evaluation of these competencies for neurosurgery residents. Material and Methods: In 2010, the Society of Neurological Surgeons (SNS) organized the first comprehensive Neurosurgery Boot Camp courses, held at six locations throughout the US and designed to assess and teach not only psychomotor skills but also components of all six Accreditation Council for Graduate Medical Education (ACGME) core competencies. These courses are comprised of various educational methodologies, including online material, faculty lectures, clinical scenario and group discussions, manual skills stations, and pre- and post-course assessments. Resident progress in each of the 6 ACGME competencies is now tracked using the neurosurgical Milestones, developed by the ACGME in collaboration with the SNS. In addition, the Milestones drafting group for neurosurgery has formulated a milestone-compatible evaluation system to directly populate Milestone reports. These evaluations utilize formative, summative, and 360-degree evaluations that are considered by a faculty core competency committee in finalizing milestones levels for each resident. Results: Initial attendance at the 2010 Boot Camp course was 94% of the incoming resident class and in subsequent years, 100%. Pre- and post-course surveys demonstrated a significant and sustained increase in knowledge. The value of these courses has been recognized by the ACGME, which requires Boot Camp or equivalent participation prior to acting with indirect supervision during clinical activities. Neurosurgery was one of 7 early Milestone adopter specialties, beginning use in July, 2013. Early milestone data will establish benchmarks prior to utilization for "high stake" decisions such as promotion, graduation, and termination. Conclusions: The full impact of the neurosurgical Boot Camps and Milestones on residency education remains to be measured, although published data from the first years of the Boot Camp Courses demonstrate broad acceptance and early effectiveness. A complementary junior resident course has now been introduced for rising second-year residents. The Milestones compatible evaluation system now provides for multi-source formative and summative evaluation of neurosurgical residents within the new ACGME reporting rubric. Combined with consensus milestone assignments, this system provides new specificity and objectivity to resident evaluations. The correlation of milestone level

assignments with other measurements of educational outcome awaits further study. © 2014 Association of Program Directors in Surgery.

Franklin, A. E., Burns, P., & Lee, C. S. (2014). Psychometric testing on the NLN student satisfaction and self-confidence in learning, simulation design scale, and educational practices questionnaire using a sample of pre-licensure novice nurses. *Nurse Education Today, 34*(10), 1298-1304.
BACKGROUND: In 2006, the National League for Nursing published three measures related to novice nurses' beliefs about self-confidence, scenario design, and educational practices associated with simulation. Despite the extensive use of these measures, little is known about their reliability and validity. METHODS: The psychometric properties of the Student Satisfaction and Self-Confidence in Learning Scale, Simulation Design Scale, and Educational Practices Questionnaire were studied among a sample of 2200 surveys completed by novice nurses from a liberal arts university in the southern United States. Psychometric tests included item analysis, confirmatory and exploratory factor analyses in randomly-split subsamples, concordant and discordant validity, and internal consistency. RESULTS: All three measures have sufficient reliability and validity to be used in education research. There is room for improvement in content validity with the Student Satisfaction and Self-Confidence in Learning and Simulation Design Scale. CONCLUSION: This work provides robust evidence to ensure that judgments made about self-confidence after simulation, simulation design and educational practices are valid and reliable.

Fu, K. -. G., Bess, S., Shaffrey, C. I., Smith, J. S., Lafage, V., Schwab, F., et al. (2014). Patients with adult spinal deformity treated operatively report greater baseline pain and disability than patients treated nonoperatively; however, deformities differ between age groups. *Spine, 39*(17), 1401-1407.
STUDY DESIGN.: Multicenter, prospective analysis of consecutive patients with adult spinal deformity (ASD). OBJECTIVE.: Identify age-related radiographical parameters associated with poor health-related quality of life (HRQOL) and treatment preferences for ASD. SUMMARY OF BACKGROUND DATA.: Patients with ASD report discrepant severities of disability. Understanding age-associated differences for reported disability and treatment preferences may improve ASD

evaluation and treatment. METHODS.: Baseline demographic, radiographical, and HRQOL values were evaluated in a multicenter, prospective cohort of consecutive patients with ASD. Inclusion criteria: ASD, age more than 18 years, and no prior spine surgery. Patients were grouped into those treated operatively (OP) or nonoperatively (NON) and stratified into 3 age groups: G1, 50 years or less; G2, 50 to 65 years; G3, 65 years or more. HRQOL measures included Scoliosis Research Society-22r questionnaire, Oswestry Disability Index, and Short Form-36 Health Survey. RESULTS.: Four hundred ninety-seven patients (OP = 156, NON = 341) with a mean age of 50.4 years met inclusion criteria. The OP group was older (53.3 vs. 49.0 yr), had larger scoliosis (49.3° vs. 43.3°), larger sagittal vertical axis (SVA, 33.2 vs. 13.7 mm), greater pelvic incidence-lumbar lordosis mismatch (6.6°vs. 3.1°), and worse HRQOL scores than the NON group, respectively ($P < 0.05$). Age stratification demonstrated worsening of SVA, spinopelvic alignment (SPA), and HRQOL scores with increasing age ($P < 0.05$). Age/treatment stratification demonstrated that younger OP had greater scoliosis than NON (G1OP = 49.9°vs. G1NON = 42.2°; G2OP = 56°vs. G2NON = 47.2°; $P < 0.05$) but similar SPA as NON. Older OP had similar scoliosis, but larger SVA than NON (G3OP = 100.6 vs. G3NON = 66.4 mm; $P < 0.05$). OP in all age groups reported worse HRQOL than NON ($P < 0.05$). CONCLUSION.: Poor HRQOL uniformly determined operative treatment for ASD. Spinal deformities differed between age groups. Younger OP had larger scoliosis but similar SPA and SVA than NON. Older OP had similar scoliosis but worse SVA than NON. Age-associated differences for poor HRQOL must be considered when evaluating patients with ASD.

Gagne, K. E., Ghazvinian, R., Yuan, D., Zon, R. L., Storm, K., Mazur-Popinska, M., et al. (2014). Pearson marrow pancreas syndrome in patients suspected to have diamond-blackfan anemia. *Blood, 124*(3), 437-440.

Pearson marrow pancreas syndrome (PS) is a multisystem disorder caused by mitochondrial DNA (mtDNA) deletions. Diamond-Blackfan anemia (DBA) is a congenital hypoproliferative anemia in which mutations in ribosomal protein genes and GATA1 have been implicated. Both syndromes share several features including early onset of severe anemia, variable nonhematologicmanifestations, sporadic genetic occurrence, and occasional spontaneous hematologic improvement. Because of the overlapping features and relative rarity of PS, we

hypothesized that some patients in whom the leading clinical diagnosis is DBA actually have PS. Here, we evaluated patient DNA samples submitted for DBA genetic studies and found that 8 (4.6%) of 173 genetically uncharacterized patients contained large mtDNA deletions. Only 2 (25%) of the patients had been diagnosedwithPSon clinical grounds subsequent to samplesubmission. We conclude that PS can be overlooked, and that mtDNA deletion testing should be performed in the diagnostic evaluation of patients with congenital anemia. © 2014 by The American Society of Hematology.

Gallun, F. J., Diedesch, A. C., Kampel, S. D., & Jakien, K. M. (2014). Corrigendum: Independent impacts of age and hearing loss on spatial release in a complex auditory environment [front. neurosci., 8 (2014) 264] DOI:10.3389/fnins.2014.00264. *Frontiers in Neuroscience,* (8 AUG)

Garcia, A. M., Wakeman, D., Lu, J., Rowley, C., Geisman, T., Butler, C., et al. (2014). Tis7 deletion reduces survival and induces intestinal anastomotic inflammation and obstruction in high fat diet-fed mice with short bowel syndrome. *American Journal of Physiology.Gastrointestinal and Liver Physiology,*

Effective therapies are limited for patients with parenteral nutrition-dependent short bowel syndrome. We previously showed that intestinal expression of the transcriptional co-regulator tis7 is markedly increased during the adaptive response following massive small bowel resection, and tis7 plays a role in normal gut lipid metabolism. Herein we further explore the functional implications of tis7 deletion on intestinal lipid metabolism and the adaptive response following small bowel resection. Methods: Tis7-/- , intestinal tis7 transgenic (tis7tg) and wild type (WT) littermates were subjected to 50% small bowel resection. Mice were fed a control or a high saturated fat (42% energy) diet for 21 days. Survival, body weight recovery, lipid absorption and the morphometric adaptive response were analyzed. QRT PCR was performed to identify tis7 downstream gene targets. Results: Post-resection survivals were markedly reduced in high fat diet-fed but not control diet-fed tis7-/- mice. Decreased survival was associated with anastomotic inflammation and intestinal obstruction post-resection. High fat diet-fed but not control diet fed tis7-/- mice had increased intestinal IL6 and NF-kappaB p65 expression compared to WTs post-resection. In contrast, high fat diet-fed tis7tg mice had improved survival post-resection

compared to WT littermates. Conclusions: High fat diet feeding in the setting of tis7 deletion resulted in a novel model of post-resection anastomotic inflammation and small bowel obstruction. Tis7 and its targets may be required for tolerance of a calorie-rich, high fat diet post-resection. The presence of luminal fat in the setting of tis7 deletion promotes an intestinal inflammatory response post resection.

Gaytan, F., Garcia-Galiano, D., Dorfman, M. D., Manfredi-Lozano, M., Castellano, J. M., Dissen, G. A., et al. (2014). Kisspeptin receptor haplo-insufficiency causes premature ovarian failure despite preserved gonadotropin secretion. *Endocrinology, 155*(8), 3088-3097.

Premature ovarian failure (POF) affects1%of women in reproductive age, but its etiology remains uncertain. Whereas kisspeptins, the products of Kiss 1 that act via Kiss1r (aka, Gpr54), are known to operate at the hypothalamus to control GnRH/gonadotropin secretion, additional actions at other reproductive organs, including the ovary, have been proposed. Yet, their physiological relevance is still unclear. We present here a series of studies in Kiss1r haplo-insufficient and null mice suggestingadirect roleofkisspeptin signalinginthe ovary, the defect ofwhich precipitates a state of primary POF. Kiss1r hypomorph mice displayed a premature decline in ovulatory rate, followed by progressive loss of antral follicles, oocyte loss, and a reduction in all categories of preantral follicles. These alterations were accompanied by reduced fertility. Because of this precocious ovarian ageing, mice more than48 weeks of age showed atrophic ovaries, lacking growing follicles and corporalutea. This phenomen on was associated with adropinovarian Kiss1rm RNA expression, but took place in the absence of a decrease in circulating gonadotropins. In fact, FSH levels increased in aged hypomorph animals, reflecting loss of follicular function. In turn, Kiss1r-null mice, which do not spontaneously ovulate and have arrested follicular development, failed to show normal ovulatory responses to standard gonadotropin priming and required GnRH prestimulation during 1 week in order to display gonadotropin-induced ovulation. Yet, the magnitude of such ovulatory responses was approximately half of that seen in control immature wild-type animals. Altogether, our data are the first to demonstrate that Kiss1r haplo-insufficiency induces a state of POF, which is not attributable to defective gonadotropin secretion. We also show that the failure of follicular development and ovulation linked to the absence of Kiss1r cannot be fully rescued by (even

extended) gonadotropin replacement. These findings suggest a direct ovarian role of kisspeptin signaling, the perturbation of which may contribute to the pathogenesis of POF. Copyright © 2014 by the Endocrine Society.

Ghazizadeh, S., Foss, E. W., Didier, R., Fung, A., Panicek, D. M., & Coakley, F. V. (2014). Musculoskeletal pitfalls and pseudotumors in the pelvis: A pictorial review for body imagers. *The British Journal of Radiology,* , 20140243.

Many musculoskeletal abnormalities in the pelvis are first seen by body imagers while reviewing pelvic cross-sectional studies, and some of these abnormalities may mimic malignancy or another aggressive process. This paper describes nine musculoskeletal pseudotumors and interpretative pitfalls that may be seen at CT, MRI, and ultrasound imaging of the pelvis. Awareness of these pitfalls and pseudotumors may help avoid misdiagnosis and prevent inappropriate intervention or management.

Giardiello, F. M., Allen, J. I., Axilbund, J. E., Boland, C. R., Burke, C. A., Burt, R. W., et al. (2014). Guidelines on genetic evaluation and management of lynch syndrome: A consensus statement by the us multi-society task force on colorectal cancer. *Diseases of the Colon and Rectum, 57*(8), 1025-1048.

Giardiello, F. M., Allen, J. I., Axilbund, J. E., Boland, C. R., Burke, C. A., Burt, R. W., et al. (2014). Guidelines on genetic evaluation and management of lynch syndrome: A consensus statement by the US multi-society task force on colorectal cancer. *The American Journal of Gastroenterology, 109*(8), 1159-1179.

The Multi-Society Task Force, in collaboration with invited experts, developed guidelines to assist health care providers with the appropriate provision of genetic testing and management of patients at risk for and affected with Lynch syndrome as follows: Figure 1 provides a colorectal cancer risk assessment tool to screen individuals in the office or endoscopy setting; Figure 2 illustrates a strategy for universal screening for Lynch syndrome by tumor testing of patients diagnosed with colorectal cancer; Figures 3,4,5,6 provide algorithms for genetic evaluation of affected and at-risk family members of pedigrees with Lynch syndrome; Table 10 provides guidelines for screening at-risk and affected persons with Lynch syndrome; and Table 12 lists the

guidelines for the management of patients with Lynch syndrome. A detailed explanation of Lynch syndrome and the methodology utilized to derive these guidelines, as well as an explanation of, and supporting literature for, these guidelines are provided.

Gong, Q., Stump, M. R., & Zhou, Z. (2014). Upregulation of functional Kv11.1 isoform expression by inhibition of intronic polyadenylation with antisense morpholino oligonucleotides. *Journal of Molecular and Cellular Cardiology,*

The KCNH2 gene encodes the Kv11.1 potassium channel that conducts the rapidly activating delayed rectifier current in the heart. KCNH2 pre-mRNA undergoes alternative processing; intron 9 splicing leads to the formation of a functional, full-length Kv11.1a isoform, while polyadenylation within intron 9 generates a non-functional, C-terminally truncated Kv11.1a-USO isoform. The relative expression of Kv11.1 isoforms plays an important role in the regulation of Kv11.1 channel function and the pathogenesis of long QT syndrome. In this study, we identified cis-acting elements that are required for KCNH2 intron 9 poly(A) signal activity. Mutation of these elements decreased Kv11.1a-USO expression and increased the expression of Kv11.1a mRNA, protein and channel current. More importantly, blocking these elements by antisense morpholino oligonucleotides shifted the alternative processing of KCNH2 intron 9 from the polyadenylation to the splicing pathway, leading to the predominant production of Kv11.1a and a significant increase in Kv11.1 current. Our findings indicate that the expression of the Kv11.1a isoform can be upregulated by an antisense approach. Antisense inhibition of KCNH2 intronic polyadenylation represents a novel approach to increase Kv11.1 channel function.

Goodman, A., Kajantie, E., Osmond, C., Eriksson, J., Koupil, I., Thornburg, K., et al. (2014). The relationship between umbilical cord length and chronic rheumatic heart disease: A prospective cohort study. *European Journal of Preventive Cardiology,*

BACKGROUND: One previous, preliminary study reported that the length of the umbilical cord at birth is related to the risk of developing chronic rheumatic heart disease in later life. We sought to replicate this finding. DESIGN: Prospective, population-based birth cohort. METHODS: We traced 11,580 individuals born between 1915 and 1929 in Uppsala, Sweden. We identified cases with a main or secondary diagnosis of chronic rheumatic heart disease in the Swedish national

inpatient, outpatient or death registers. Archived obstetric records provided data on umbilical cord length, gestational age, birthweight and placental weight. RESULTS: There were 136 patients with chronic rheumatic heart disease (72 men and 64 women) with a mean age at first hospital admission of 68 years (range 36-92). There was evidence of a positive association between umbilical cord length and risk of subsequent chronic rheumatic heart disease. The overall hazard ratio in the Swedish study (1.13, 95% confidence interval 1.01 to 1.27) was similar to that of the previous study, with some suggestion of larger effect in men than in women. No other birth characteristics were predictive except for weak evidence of a protective effect of higher birthweight in men. CONCLUSIONS: People with longer umbilical cords at birth are more likely to develop chronic rheumatic heart disease in later life. As longer umbilical cords have more spiral arteries and a higher vascular resistance, we hypothesize that the increased pressure load on the heart leads to changes in endothelial biology and increased vulnerability to the autoimmune process initiated by infection with beta-haemolytic streptococci.

Goodworth, A. D., Mellodge, P., & Peterka, R. J. (2014). Stance width changes how sensory feedback is used for multisegmental balance control. *Journal of Neurophysiology, 112*(3), 525-542.

A multilink sensorimotor integration model of frontal plane balance control was developed to determine how stance width influences the use of sensory feedback in healthy adults. Data used to estimate model parameters came from seven human participants who stood on a continuously rotating surface with three different stimulus amplitudes, with eyes open and closed, and at four different stance widths. Dependent variables included lower body (LB) and upper body (UB) sway quantified by frequency-response functions. Results showed that stance width had a major influence on how parameters varied across stimulus amplitude and between visual conditions. Active mechanisms dominated LB control. At narrower stances, with increasing stimulus amplitude, subjects used sensory reweighting to shift reliance from proprioceptive cues to vestibular and/or visual cues that oriented the LB more toward upright. When vision was available, subjects reduced reliance on proprioception and increased reliance on vision. At wider stances, LB control did not exhibit sensory reweighting. In the UB system, both active and passive mechanisms contributed and were dependent on stance width. UB control changed across stimulus amplitude most in wide stance (opposite of the pattern found in LB control). The strong

influence of stance width on sensory integration and neural feedback control implies that rehabilitative therapies for balance disorders can target different aspects of balance control by using different stance widths. Rehabilitative strategies designed to assess or modify sensory reweighting will be most effective with the use of narrower stances, whereas wider stances present greater challenges to UB control. © 2014 the American Physiological Society.

Gordon, N. T., & Schreiber, M. A. (2014). Frozen blood and lessons learned from 9/11. *The Journal of Trauma and Acute Care Surgery, 77*(3), 479-485.

Gu, Q., Koenig, L., Mather III, R. C., & Tongue, J. (2014). Surgery for hip fracture yields societal benefits that exceed the direct medical costs. *Clinical Orthopaedics and Related Research®,* Background A hip fracture is a debilitating condition that consumes significant resources in the United States. Surgical treatment of hip fractures can achieve better survival and functional outcomes than nonoperative treatment, but less is known about its economic benefits. Questions/purposes We asked: (1) Are the societal benefits of hip fracture surgery enough to offset the direct medical costs? (2) Nationally, what are the total lifetime benefits of hip fracture surgery for a cohort of patients and to whom do these benefits accrue? Methods We estimated the effects of surgical treatment for displaced hip fractures through a Markov cohort analysis of patients 65 years and older. Assumptions were obtained from a systematic literature review, analysis of Medicare claims data, and clinical experts. We conducted a series sensitivity analyses to assess the effect of uncertainty in model parameters on our estimates. We compared costs for medical care, home modification, and long-term nursing home use for surgical and nonoperative treatment of hip fractures to estimate total societal savings. Results Estimated average lifetime societal benefits per patient exceeded the direct medical costs of hip fracture surgery by USD 65,000 to USD 68,000 for displaced hip fractures. With the exception of the assumption of nursing home use, the sensitivity analyses show that surgery produces positive net societal savings with significant deviations of 50% from the base model assumptions. For an 80-year-old patient, the breakeven point for the assumption on the percent of patients with hip fractures who would require long-term nursing home use with nonoperative treatment is 37% to 39%, compared with 24% for surgical patients. Nationally, we estimate that hip fracture surgery for the

cohort of patients in 2009 yields lifetime societal savings of USD 16 billion in our base model, with benefits and direct costs of USD 21 billion and USD 5 billion, respectively. For an 80-year-old, societal benefits ranged from USD 2 billion to USD 32 billion, using our range of estimates for nursing home use among nonoperatively treated patients who are immobile after the fracture. Conclusions Surgical treatment of hip fractures produces societal savings. Although the magnitude of these savings depends on model assumptions, the finding of societal savings is robust to a range of parameter values. Level of Evidence Level III, economic and decision analyses. See the Instructions for Authors for a complete description of levels of evidence. © 2014 The Author(s).

Guo, J., Tretiakova, M. S., Troxell, M. L., Osunkoya, A. O., Fadare, O., Sangoi, A. R., et al. (2014). Tuberous sclerosis-associated renal cell carcinoma: A clinicopathologic study of 57 separate carcinomas in 18 patients. *The American Journal of Surgical Pathology,*

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with characteristic tumors involving multiple organ systems. Whereas renal angiomyolipoma (AML) is common in TSC, renal cell carcinoma (RCC) is rarely reported. Fifty-seven RCCs from 13 female and 5 male TSC patients were reviewed. Age at surgery ranged from 7 to 65 years (mean: 42 y). Nine patients (50%) had multiple synchronous and/or metachronous RCCs (range of 2 to 20 RCCs) and 5 had bilateral RCCs (28%). Seventeen patients (94%) had histologically confirmed concurrent renal AMLs, including 15 with multiple AMLs (88%) and 9 (50%) with AMLs with epithelial cysts. None of the 15 patients with available clinical follow-up information had evidence of distant metastatic disease from 6 to 198 months after their initial surgery (mean: 52 mo). The 57 RCCs exhibited 3 major distinct morphologies: (1) 17 RCCs (30%) had features similar to tumors previously described as "renal angiomyoadenomatous tumor" or "RCC with smooth muscle stroma"; (2) 34 RCCs (59%) showed features similar to chromophobe RCC; and (3) 6 RCCs (11%) showed a granular eosinophilic-macrocystic morphology. Distinct histologic changes were also commonly present in the background kidney parenchyma and included cysts or renal tubules lined by epithelial cells with prominent eosinophilic cytoplasm, nucleomegaly, and nucleoli. Immunohistochemically, all RCCs tested showed strong nuclear reactivity for PAX8 and HMB45 negativity. Compared with sporadic RCCs, TSC-associated RCCs have unique clinicopathologic

features including female predominance, younger age at diagnosis, multiplicity, association with AMLs, 3 recurring histologic patterns, and an indolent clinical course. Awareness of the morphologic and clinicopathologic spectrum of RCC in this setting will allow surgical pathologists to better recognize clinically unsuspected TSC patients.

Haberthur, K., Meyer, C., Arnold, N., Engelmann, F., Jeske, D. R., & Messaoudi, I. (2014). Intrabronchial infection of rhesus macaques with simian varicella virus results in a robust immune response in the lungs. *Journal of Virology,*

Varicella zoster virus (VZV) is the etiological agent of varicella (chickenpox) and herpes zoster (shingles). Primary VZV infection is believed to occur via the inhalation of virus either in respiratory droplets, from shedding varicella lesions or by direct contact with infectious vesicular fluid. However, the ensuing immune response in the lungs remains incompletely understood. We have shown that intrabronchial inoculation of rhesus macaques with simian varicella virus (SVV), a homolog of VZV, recapitulates the hallmarks of acute and latent VZV infection in humans. In this study, we performed an in-depth analysis of the host immune response to acute SVV infection in the lungs and peripheral blood. We report that acute SVV infection results in a robust innate immune response in the lungs, characterized by the production of inflammatory cytokines, chemokines, and growth factors as well as an increased frequency of plasmacytoid DCs that corresponded with IFNalpha production and a rapid decrease in viral loads in the lungs. This is followed by T and B cell proliferation, antibody production, T cell differentiation and cytokine production, which correlate with the complete cessation of viral replication. Although terminally differentiated CD8 T cells became the predominant T cell population in bronchoalveolar lavage cells, a higher percentage of CD4 T cells were SVV-specific, which suggests a critical role for these cells in the resolution of primary SVV infection in the lungs. Given the homology between SVV and VZV, our data provide insight into the immune response to VZV within the lung. IMPORTANCE: Although primary VZV infection occurs primarily via the respiratory route, our understanding of the host response in the lungs and its contribution to the cessation of viral replication and establishment of latency remains poorly understood. The difficulty in accessing lung tissue and washes from individuals infected with VZV has hampered efforts to address this knowledge gap. SVV infection of rhesus macaques is an important model of VZV infection of

humans; therefore we utilized this animal model to gain a comprehensive view of the kinetics of the immune response to SVV in the lung and its relationship to the resolution of acute infection in respiratory tissues. These data not only advance our understanding of host immunity to VZV, a critical step in developing new vaccines, but also provide additional insight into immunity to respiratory pathogens.

Hadd, A., & Perona, J. J. (2014). Coevolution of specificity determinants in eukaryotic glutamyl- and glutaminyl-tRNA synthetases. *Journal of Molecular Biology,*

The glutaminyl-tRNA synthetase (GlnRS) enzyme, which pairs glutamine with tRNAGln for protein synthesis, evolved by gene duplication in early eukaryotes from a nondiscriminating glutamyl-tRNA synthetase (GluRS) that aminoacylates both tRNAGln and tRNAGlu with glutamate. This ancient GluRS also separately differentiated to exclude tRNAGln as a substrate, and the resulting discriminating GluRS and GlnRS further acquired additional protein domains assisting function in cis (the GlnRS N-terminal Yqey domain) or in trans (the Arc1p protein associating with GluRS). These added domains are absent in contemporary bacterial GlnRS and GluRS. Here, using Saccharomyces cerevisiae enzymes as models, we find that the eukaryote-specific protein domains substantially influence amino acid binding, tRNA binding and aminoacylation efficiency, but they play no role in either specific nucleotide readout or discrimination against noncognate tRNA. Eukaryotic tRNAGln and tRNAGlu recognition determinants are found in equivalent positions and are mutually exclusive to a significant degree, with key nucleotides located adjacent to portions of the protein structure that differentiated during the evolution of archaeal nondiscriminating GluRS to GlnRS. These findings provide important corroboration for the evolutionary model and suggest that the added eukaryotic domains arose in response to distinctive selective pressures associated with the greater complexity of the eukaryotic translational apparatus. We also find that the affinity of GluRS for glutamate is significantly increased when Arc1p is not associated with the enzyme. This is consistent with the lower concentration of intracellular glutamate and the dissociation of the Arc1p:GluRS complex upon the diauxic shift to respiratory conditions.

Haderlein, S. B., Grundl, T. J., & Tratnyek, P. G. (2011). *Preface* American Chemical Society.

Hakki, M., Goldman, D. C., Streblow, D. N., Hamlin, K. L., Krekylwich, C. N., Fleming, W. H., et al. (2014). HCMV infection of humanized mice after transplantation of G-CSF-mobilized peripheral blood stem cells from HCMV-seropositive donors. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation, 20*(1), 132-135.

Human cytomegalovirus (HCMV) infection, including primary infection resulting from transmission from a seropositive donor to a seronegative recipient (D(+)/R(-)), remains a significant problem in the setting of peripheral blood stem cell transplantation (PBSCT). The lack of a suitable animal model for studying HCMV transmission after PBSCT is a major barrier to understanding this process and, consequently, developing novel interventions to prevent HCMV infection. Our previous work demonstrated that human CD34(+) progenitor cell-engrafted NOD-scid IL2Rgammac(null) (NSG) mice support latent HCMV infection after direct inoculation and reactivation after treatment with granulocyte colony-stimulating factor. To more accurately recapitulate HCMV infection in the D(+)/R(-) PBSCT setting, granulocyte colony-stimulating factor-mobilized peripheral blood stem cells from seropositive donors were used to engraft NSG mice. All recipient mice demonstrated evidence of HCMV infection in liver, spleen, and bone marrow. These findings validate the NSG mouse model for studying HCMV transmission during PBSCT.

Hakki, M., Strasfeld, L. M., & Townes, J. M. (2014). Predictive value of nasopharyngeal sample respiratory virus testing in the setting of lower respiratory tract disease. *Journal of Clinical Microbiology,*

To determine the predictive value of nasopharyngeal (NP) sample testing for respiratory viruses (RVs) in suspected lower respiratory tract disease, 72 paired NP and bronchoalveolar lavage (BAL) specimen sets, mostly from transplant recipients or patients with hematologic malignancies, were analyzed. 31.3% of specimens tested positive for an RV. Nineteen sets (26.4%) were NP+/BAL+, three (4.2%) were NP+/BAL-, and three were NP-/BAL+. The positive and negative predictive value of NP specimens was 86.4% and 94%, respectively.

Hamill, E. B., Agrawal, M., Diwan, A. H., Winthrop, K. L., & Marx, D. P. (2014). Angiosarcoma of the eyelid with superimposed enterobacter infection. *Ophthalmic Plastic and Reconstructive Surgery,*

Angiosarcoma is a rare, aggressive, malignant endothelial neoplasm with a variable clinical presentation. The authors describe a case of angiosarcoma involving the eyelid that was complicated by a superimposed Enterobacter infection. Following positive cultures for E. aerogenes and multiple biopsies suspicious but not definitive for angiosarcoma, a final biopsy was consistent with angiosarcoma.

Hansen, L., Rosenkranz, S. J., Vaccaro, G. M., & Chang, M. F. (2014). Patients with hepatocellular carcinoma near the end of life: A longitudinal qualitative study of their illness experiences. *Cancer Nursing,*

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.

Hartley, M. D., Altowaijri, G., & Bourdette, D. (2014). Remyelination and multiple sclerosis: Therapeutic approaches and challenges. *Current Neurology and Neuroscience Reports, 14*(10), 485-014-0485-1.

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system. After acute inflammatory mediated demyelination, some remyelination often occurs, but in chronic demyelinated MS plaques, remyelination frequently fails. Chronically demyelinated axons cause a variety of symptoms and probably are more likely to degenerate, leading to irreversible clinical disability. Oligodendrocyte precursor cells (OPCs) present in the adult brain can proliferate and differentiate to remyelinate lesions. Failure of remyelination in the majority of MS patients is secondary to arrest in OPC differentiation. Many therapies have been developed to modulate the immune response in MS, but no neuroprotective or remyelinating therapies are available. Promoting remyelination is a promising avenue for protecting axons, reversing neurologic disability and preventing progressive disease in MS. This review will begin with an overview of remyelination and remyelination failure, consequences of demyelination, and available animal disease models. In addition, preclinical and clinical studies on the most promising potential therapies for inducing remyelination will be described.

Hayflick, S. J. (2014). Defective pantothenate metabolism and neurodegeneration. *Biochemical Society Transactions, 42*(4), 1063-1068.

Inborn errors of CoA (coenzyme A) biosynthesis lead to neurodegenerative disorders in humans. PKAN (pantothenate kinase-associated neurodegeneration) manifests with damage to brain, retina and testis and is caused by mutations in PANK2, the gene encoding the mitochondrial form of pantothenate kinase, a key regulatory enzyme in CoA synthesis. Further attention has been focused on this pathway by the recent discovery that mutations in the gene encoding CoA synthase lead to a similar neurodegenerative disorder, raising the spectre of a common mechanism of pathogenesis. How do defects in CoA production result in neurodegeneration? Why are certain tissues and cell types selectively vulnerable? And what is the underlying neurodegenerative process? Answers to some of these questions have come from animal models of disease, including flies and mice, as well as directly from humans. The damaged tissue types share key features that are likely to contribute to their selective vulnerability. These include the

presence of a blood-tissue barrier, the milieu with respect to oxidative stress, tissue metabolic demand, relative expression of genes encoding similar proteins in these tissues and cell membrane composition. Substantial progress in understanding these important neurometabolic disorders has been made since the first gene discovery more than a decade ago. With rational therapeutics now in development for PKAN, we foresee prevention of neurodegeneration and hope for neuroregeneration or neuro-rescue. © The Authors Journal compilation © 2014 Biochemical Society.

He, W. -., Li, Y. -., Hou, W. -., Ke, Z. -., Chen, X. -., Lu, L. -., et al. (2014). RAD51 potentiates synergistic effects of chemotherapy with PCI-24781 and cis-diamminedichloroplatinum on gastric cancer. *World Journal of Gastroenterology, 20*(29), 10094-10107.

AIM: To explore the efficacy of PCI-24781, a broadspectrum, hydroxamic acid-derived histone deacetylase inhibitor, in the treatment of gastric cancer (GC). METHODS: With or without treatment of PCI-24781 and/or cis-diamminedichloroplatinum (CDDP), GC cell lines were subjected to functional analysis, including cell growth, apoptosis and clonogenic assays. Chromatin immunoprecipitation and luciferase reporter assays were used to determine the interacting molecules and the activity of the enzyme. An in vivo study was carried out in GC xenograft mice. Cell culture-based assays were represented as mean ± SD. ANOVA tests were used to assess differences across groups. All pairwise comparisons between tumor weights among treatment groups were made using the Tukey-Kramer method for multiple comparison adjustment to control experimental-wise type I error rates. Significance was set at $P < 0.05$. RESULTS: PCI-24781 significantly reduced the growth of the GC cells, enhanced cell apoptosis and suppressed clonogenicity, and these effects synergized with the effects of CDDP. PCI-24781 modulated the cell cycle and significantly reduced the expression of RAD51, which is related to homologous recombination. Depletion of RAD51 augmented the biological functions of PCI-24781, CDDP and the combination treatment, whereas overexpressing RAD51 had the opposite effects. Increased binding of the transcription suppressor E2F4 on the RAD51 promoter appeared to play a major role in these processes. Furthermore, significant suppression of tumor growth and weight in vivo was obtained following PCI-24781 treatment, which synergized with the anticancer effect

of CDDP. CONCLUSION: These data suggest that RAD51 potentiates the synergistic effects of chemotherapy with PCI-24781 and CDDP on GC.

Heckman, B. D., Lovejoy, T. I., Heckman, T. G., Anderson, T., Grimes, T., Sutton, M., et al. (2014). The moderating role of sexual identity in group teletherapy for adults aging with HIV. *Behavioral Medicine, 40*(3), 134-142.

Older adults living with HIV/AIDS experience high rates of depression and suicidal ideation but are less likely than their younger counterparts to seek psychological services. HIV continues to disproportionately impact older men who have sex with men (MSM), many of whom were infected in their 20s and 30s. This study examined whether therapy attendance rates and the efficacies of two group-format teletherapies for the treatment of depression (coping effectiveness group training and supportive-expressive group therapy) were comparable for older MSM and older heterosexuals living with HIV. Intervention-outcome analyses found that older MSM and older heterosexuals living with HIV attended comparable numbers of teletherapy sessions. Older heterosexuals living with HIV who received telephone-administered supportive-expressive group therapy reported significantly greater reductions in depressive symptoms than SOC controls. A similar pattern was not found in older MSM. More research is needed to personalize and tailor group teletherapies for older MSM living with HIV.

Heintzman, J., Marino, M., Hoopes, M., Bailey, S., Gold, R., Crawford, C., et al. (2014). Using electronic health record data to evaluate preventive service utilization among uninsured safety net patients. *Preventive Medicine,*

OBJECTIVE: This study compared the preventive service utilization of uninsured patients receiving care at Oregon community health centers (CHCs) in 2008 through 2011 with that of continuously insured patients at the same CHCs in the same period, using electronic health record (EHR) data. METHODS: We performed a retrospective cohort analysis, using logistic mixed effects regression modeling to calculate odds ratios and rates of preventive service utilization for patients without insurance, or with continuous insurance. RESULTS: CHCs provided many preventive services to uninsured patients. Uninsured patients were less likely than continuously

insured patients to receive 5 of 11 preventive services, ranging from OR 0.52 (95% CI: 0.35-0.77) for mammogram orders to 0.75 (95% CI: 0.66-0.86) for lipid panels. This disparity persisted even in patients who visited the clinic regularly. CONCLUSION: Lack of insurance is a barrier to preventive service utilization, even in patients who can access care at a CHC. Policymakers in the United States should continue to address this significant prevention disparity.

Heppner, K. M., & Tong, J. (2014). Mechanisms in endocrinology: Regulation of glucose metabolism by the ghrelin system: Multiple players and multiple actions. *European Journal of Endocrinology / European Federation of Endocrine Societies, 171*(1), R21-32.

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

Hoadley, K. A., Yau, C., Wolf, D. M., Cherniack, A. D., Tamborero, D., Ng, S., et al. (2014). Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. *Cell,*

Recent genomic analyses of pathologically defined tumor types identify "within-a-tissue" disease subtypes. However, the extent to which genomic signatures are shared across tissues is still unclear. Weperformed an integrative analysis using five genome-wide platforms and one proteomic platform on 3,527 specimens from 12 cancer types, revealing a unified classification into 11 major subtypes. Five subtypes were nearly identical to their tissue-of-origin counterparts, but several distinct cancer types were found to converge into common subtypes. Lungsquamous, head and neck, and a subset of bladder cancers coalesced into one subtype typified by TP53

alterations, TP63 amplifications, and high expression of immune and proliferation pathway genes. Of note, bladder cancers split into three pan-cancer subtypes. The multiplatform classification, while correlated with tissue-of-origin, provides independent information for predicting clinical outcomes. All data sets are available for data-mining from a unified resource to support further biological discoveries and insights into novel therapeutic strategies. Integrated genomic and computational analysis across data from 12 tumor types reveals that differences between tumors largely track with tissue of origin, but that molecular data integration provides new prognostic information. Integrated clustering reveals 11 major subtypes that reclassify 10% of tumors and indicates pathway activity differences among tumors with common genomic lesions. © 2014 Elsevier Inc.

Hopkins, R., Pratt, D., Bowen, J. L., & Regehr, G. (2014). Integrating basic science without integrating basic scientists: Reconsidering the place of individual teachers in curriculum reform. *Academic Medicine : Journal of the Association of American Medical Colleges,*

The call for integration of the basic and clinical sciences plays prominently in recent conversations about curricular change in medical education; however, history shows that, like other concepts related to curricular reform, integration has been continually revisited, leading to incremental change but no meaningful transformation. To redress this cycle of "change without difference," the medical education community must reexamine the approach that dominates medical education reform efforts and explore alternative perspectives that may help to resolve the cyclical "problem" of recommending but not effecting integration. To provide a different perspective on implementing integration, the authors of this Perspective look to the domain of educational change as an approach to examining the transitions that occur within complex and evolving environments. This area of literature both acknowledges the multiple levels involved in change and emphasizes the need not only to address systemic structure but also to prioritize individuals during times of transition. The struggle to implement curricular integration in medical education may stem from the fact that reform efforts appear to focus largely on transformation at the level of curricular structure as opposed to considering what learning needs to occur at each level of change and highlighting the individual as the educational change literature suggests. To bring appropriate attention to the place of individual educators, especially basic scientists, the medical

education community should explore how the mandate to integrate clinically relevant material may impact these faculty and the teaching of their domains.

Horner-Johnson, W., Dobbertin, K., Lee, J. C., & Andresen, E. M. (2014). Rural disparities in receipt of colorectal cancer screening among adults ages 50-64 with disabilities. *Disability and Health Journal,*

BACKGROUND: Colorectal cancer is the third leading cause of cancer deaths in the United States. Early detection can reduce mortality; however, only 59% of U.S. adults age 50 and over meet recommended colorectal cancer screening guidelines. Studies in the general population have observed that rural residents are less likely to have received colorectal cancer screening than residents of urban areas. OBJECTIVE: To determine whether urban/rural disparities in colorectal cancer screening exist among people with disabilities, similar to the disparities found in the general population. METHODS: We analyzed Medical Expenditure Panel Survey annual data files from 2002 to 2008. We conducted logistic regression analyses to examine the relationship between urban/rural residence and ever having received screening for colorectal cancer (via colonoscopy, sigmoidoscopy, or fecal occult blood test). RESULTS: Among U.S. adults ages 50-64 with disabilities, those living in rural areas were significantly less likely to have ever received any type of screening for colorectal cancer. The urban/rural difference was statistically significant regardless of whether or not we controlled for demographic, socioeconomic, health, and health care access variables. CONCLUSIONS: Disparity in screening for colorectal cancer places rural residents with disabilities at greater risk for late stage diagnosis and mortality relative to people with disabilities in urban areas. Thus, there is a need for strategies to improve screening among people with disabilities in rural areas.

Hunnicutt, B. J., Long, B. R., Kusefoglu, D., Gertz, K. J., Zhong, H., & Mao, T. (2014). A comprehensive thalamocortical projection map at the mesoscopic level. *Nature Neuroscience, 17*(9), 1276-1285.

The thalamus relays sensori-motor information to the cortex and is an integral part of cortical executive functions. The precise distribution of thalamic projections to the cortex is poorly characterized, particularly in mouse. We employed a systematic, high-throughput viral approach

to visualize thalamocortical axons with high sensitivity. We then developed algorithms to directly compare injection and projection information across animals. By tiling the mouse thalamus with 254 overlapping injections, we constructed a comprehensive map of thalamocortical projections. We determined the projection origins of specific cortical subregions and verified that the characterized projections formed functional synapses using optogenetic approaches. As an important application, we determined the optimal stereotaxic coordinates for targeting specific cortical subregions and expanded these analyses to localize cortical layer-preferential projections. This data set will serve as a foundation for functional investigations of thalamocortical circuits. Our approach and algorithms also provide an example for analyzing the projection patterns of other brain regions.

Ibele, A. R., Bendewald, F. P., Mattar, S. G., & McKenna, D. T. (2014). Erratum to: Incidence of gastrojejunostomy stricture in laparoscopic roux-en-Y gastric bypass using an autologous fibrin sealant. *Obesity Surgery,*

Ilgen, J. S., Bowen, J. L., & Eva, K. W. (2014). Reflecting upon reflection in diagnostic reasoning. *Academic Medicine : Journal of the Association of American Medical Colleges, 89*(9), 1195-1196.

Jacobs, M. A., Weinstein, S., Hope, T. A., Aslam, R., Yee, J., & Coakley, F. (2014). Neuroendocrine tumors: Beyond the abdomen. *Journal of Computer Assisted Tomography,*
Several classification systems for neuroendocrine tumors (NETs) exist, which use variable terminology and criteria for grading and staging. This variability in terminology can cause confusion and difficulty in recognizing which tumors are, in fact, members of this heterogeneous group of malignancies. The largest group of NETs, the gastroenteropancreatic NETs, has been well described and characterized; however, there are less-recognized extra-abdominal NETs that can arise from nearly any organ in the body. In this article, the clinical features and imaging appearances of the extra-abdominal NETs will be reviewed, compared, and contrasted. This diverse group consists of paragangliomas, Merkel cell carcinomas, esthesioneuroblastomas, NETs of the lung, and medullary thyroid carcinomas. Recognition of these tumors as part of the larger group of NETs is important for understanding how best to approach imaging for their diagnosis, staging, and potential treatment. Familiarity with the computed tomographic and magnetic

resonance imaging appearances and the role of radionuclide imaging of these heterogeneous groups aids in the correct diagnosis and in treatment planning.

Jacobsen, H. B., Reme, S. E., Sembajwe, G., Hopcia, K., Stiles, T. C., Sorensen, G., et al. (2014). Work stress, sleep deficiency, and predicted 10-year cardiometabolic risk in a female patient care worker population. *American Journal of Industrial Medicine, 57*(8), 940-949.

Objectives: The aim of this study was to investigate the longitudinal effect of work-related stress, sleep deficiency, and physical activity on 10-year cardiometabolic risk among an all-female worker population. Methods: Data on patient care workers (n=99) was collected 2 years apart. Baseline measures included: job stress, physical activity, night work, and sleep deficiency. Biomarkers and objective measurements were used to estimate 10-year cardiometabolic risk at follow-up. Significant associations (P<0.05) from baseline analyses were used to build a multivariable linear regression model. Results: The participants were mostly white nurses with a mean age of 41 years. Adjusted linear regression showed that having sleep maintenance problems, a different occupation than nurse, and/or not exercising at recommended levels at baseline increased the 10-year cardiometabolic risk at follow-up. Conclusions: In female workers prone to work-related stress and sleep deficiency, maintaining sleep and exercise patterns had a strong impact on modifiable 10-year cardiometabolic risk. Am. J. Ind. Med. 57:940-949, 2014. © 2014 Wiley Periodicals, Inc.

Jiang, Y., Hayashi, T., Matsumura, H., Do, L. H., Majumdar, A., Lippard, S. J., et al. (2014). Light-induced NO production from a non-heme iron-nitrosyl dimer. *Journal of the American Chemical Society,*

Two non-heme iron-nitrosyl species, [Fe2(N-Et-HPTB)(O2CPh)(NO)2](BF4)2 (1a) and [Fe2(N-Et-HPTB)(DMF)2(NO)(OH)](BF4)3 (2a), are characterized by FTIR and resonance Raman spectroscopy. Binding of NO is reversible in both complexes, which are prone to NO photolysis under visible light illumination. Photoproduction of N2O occurs in high yield for 1a but not 2a. Low-temperature FTIR photolysis experiments with 1a in acetonitrile do not reveal any intermediate species, but in THF at room temperature, a new {FeNO}7 species quickly forms under illumination and exhibits a nu(NO) vibration indicative of nitroxyl-like character. This

metastable species reacts further under illumination to produce N2O. A reaction mechanism is proposed, and implications for NO reduction in flavodiiron proteins are discussed.

Joshi, N. K., Yarris, L. M., Doty, C. I., & Lin, M. (2014). Social media responses to the annals of emergency medicine residents' perspective article on multiple mini-interviews. *Annals of Emergency Medicine, 64*(3), 320-325.

In May 2014, Annals of Emergency Medicine continued a successful collaboration with an academic Web site, Academic Life in Emergency Medicine (ALiEM) to host an online discussion session featuring the 2014 Annals Residents' Perspective article "Does the Multiple Mini-Interview Address Stakeholder Needs? An Applicant's Perspective" by Phillips and Garmel. This dialogue included Twitter conversations, a live videocast with the authors and other experts, and detailed discussions on the ALiEM Web site's comment section. This summary article serves the dual purpose of reporting the qualitative thematic analysis from a global online discussion and the Web analytics for our novel multimodal approach. Social media technologies provide a unique opportunity to engage with a diverse audience to detect existing and new emerging themes. Such technologies allow rapid hypothesis generation for future research and enable more accelerated knowledge translation.

Kahn, H. S., El Ghormli, L., Jago, R., Foster, G. D., McMurray, R. G., Buse, J. B., et al. (2014). Cardiometabolic risk assessments by body mass index z-score or waist-to-height ratio in a multiethnic sample of sixth-graders. *Journal of Obesity, 2014*, 421658.

Convention defines pediatric adiposity by the body mass index z-score (BMIz) referenced to normative growth charts. Waist-to-height ratio (WHtR) does not depend on sex-and-age references. In the HEALTHY Study enrollment sample, we compared BMIz with WHtR for ability to identify adverse cardiometabolic risk. Among 5,482 sixth-grade students from 42 middle schools, we estimated explanatory variations (R (2)) and standardized beta coefficients of BMIz or WHtR for cardiometabolic risk factors: insulin resistance (HOMA-IR), lipids, blood pressures, and glucose. For each risk outcome variable, we prepared adjusted regression models for four subpopulations stratified by sex and high versus lower fatness. For HOMA-IR, R (2) attributed to BMIz or WHtR was 19%-28% among high-fatness and 8%-13% among lower-fatness students. R

(2) for lipid variables was 4%-9% among high-fatness and 2%-7% among lower-fatness students. In the lower-fatness subpopulations, the standardized coefficients for total cholesterol/HDL cholesterol and triglycerides tended to be weaker for BMIz (0.13-0.20) than for WHtR (0.17-0.28). Among high-fatness students, BMIz and WHtR correlated with blood pressures for Hispanics and whites, but not black boys (systolic) or girls (systolic and diastolic). In 11-12 year olds, assessments by WHtR can provide cardiometabolic risk estimates similar to conventional BMIz without requiring reference to a normative growth chart.

Kambham, N., Higgins, J. P., Sundram, U., & Troxell, M. L. (2014). Hematopoietic stem cell transplantation: Graft versus host disease and pathology of gastrointestinal tract, liver, and lung. *Advances in Anatomic Pathology, 21*(5), 301-320.

Hematopoietic stem cell transplantation (HCT), formerly known as bone marrow transplantation, is an integral part of treatment for many hematological malignancies. HCT is associated with several complications and comorbidities with differential effects on a wide spectrum of organs and tissues. We present an update on HCT-associated complications such as graft versus host disease (GVHD) and infection, with focus on the surgical pathology of the gastrointestinal (GI) tract, liver, and lung. Although the grading system for GI tract acute GVHD was proposed 40 years ago, recent studies have shed light on minimal histologic criteria for diagnosis of GVHD, as well as its differential diagnosis, including histologic effects of various medications. GI dysfunction in autologous transplant recipients is increasingly appreciated and patients are often biopsied. Acute liver injury in HCT is often due to sinusoidal obstruction syndrome (previously known as venoocclusive disease), or acute GVHD. Liver dysfunction at later time posttransplantation may be associated with acute or chronic GVHD, iron overload, or other causes of hepatitis. Lung injury in HCT is multifactorial, and it remains crucially important to diagnose and treat pulmonary infections. The pulmonary biopsy yields clinically unsuspected diagnoses in the majority of cases and its utilization is likely to increase. The pathology of the skin and kidney in HCT patients are detailed in accompanying articles.

Kea, B., Fu, R., Deyo, R. A., & Sun, B. C. (2014). Are discharge prescriptions of opioids from the emergency department truly rising? *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine, 21*(8), 946.

Kendrick, S. L., Redd, L., Muranyi, A., Henricksen, L. A., Stanislaw, S., Smith, L. M., et al. (2014). BCL2 antibodies targeted at different epitopes detect varying levels of protein expression and correlate with frequent gene amplification in diffuse large B-cell lymphoma. *Human Pathology,* Patients with aggressive, BCL2 protein-positive (+) diffuse large B-cell lymphoma (DLBCL) often experience rapid disease progression that is refractory to standard therapy. However, there is potential for false-negative staining of BCL2 using the standard monoclonal mouse 124 antibody that hinders the identification of these high-risk DLBCL patients. Herein, we compare 2 alternative rabbit monoclonal antibodies (E17 and SP66) to the 124 clone in staining for BCL2 in formalin-fixed, paraffin-embedded DLBCL tissues. Overall, in 2 independent DLBCL cohorts, E17 and SP66 detected BCL2 expression more frequently than 124. In the context of MYC expression, cases identified as BCL2 (+) with SP66 demonstrated the strongest correlation with worse overall survival. The 124 clone failed to detect BCL2 expression in the majority of translocation (+), amplification (+), and activated B-cell DLBCL cases in which high levels of BCL2 protein are expected. Using dual in situ hybridization as a new tool to detect BCL2 translocation and amplification, we observed similar results as previously reported for fluorescence in situ hybridization for translocation but a higher amplification frequency, indicating that BCL2 amplification may be underreported in DLBCL. Among the discrepant cases, phosphorylation of BCL2 at T69 and/or S70 was more common than in the concordant cases and may contribute to the 124 false negatives, in addition to previously associated mutations within the epitope region. The accurate detection of BCL2 expression is important in the prognosis and treatment of DLBCL particularly with new anti-BCL2 therapies.

Keyashian, K. (2014). Does endoscopic assessment of mucosal healing affect IBD management? *Digestive Diseases and Sciences,*

King, L. A., Priest, K. C., Nutt, J., Chen, Y., Chen, Z., Melnick, M., et al. (2014). Comorbidity and functional mobility in persons with parkinson's disease. *Archives of Physical Medicine and*

Rehabilitation,

OBJECTIVE: To report the frequency, severity, and types of comorbidities in people with Parkinson's disease (PD) using a validated self-report comorbidity-screening tool and to determine the relationship between comorbidity and functional mobility. DESIGN: A secondary analysis and cross-sectional observational study design. SETTING: University hospital; outpatient Balance Disorders Laboratory. PARTICIPANTS: Seventy-six persons with mild to moderate idiopathic PD. Intervention: Not Applicable. MAIN OUTCOME MEASURES: The Cumulative Illness Rating Scale-Geriatric (CIRS-G) and a comprehensive mobility assessment including gait (distance walked in 3 minutes), balance (Mini-BESTest), and physical function (Physical Performance Test). RESULTS: All participants reported comorbidities in addition to their diagnosed PD. The average number of comorbidities was 6.96 +/- 2.0 (range 2-11) and total CIRS-G score was 12.7 (+/-4.8). The most commonly reported organ systems with comorbidity were Eyes & Ears (89%), Psychiatric (68%), Musculoskeletal (64%), Lower GI (62%), Respiratory (60.5%), Upper GI (59.2%), and Genitourinary (53.9%). The total CIRS-G score was significantly related to functional mobility: gait (r=-0.53; p=0.0001), balance (r=-0.43; p=0.0003) and Physical Performance (r=-0.36; p=0.0041). Of the original 14 organ systems measured, there were 7 systems that, when combined, best predicted gait performance; 6 systems combined best-predicted balance performance and 4 systems combined that predicted functional performance. CONCLUSION: This study reports high frequency of multiple medical system comorbidity in people with mild to moderate PD. Furthermore, comorbidity scores were associated with mobility disability: gait, balance and physical function. Early intervention is important to delay mobility disability in PD and we recommend that people with PD found to have comorbidities should be screened for balance and gait deficits.

Kiriakis, J., Gaich, N., Claiborne Johnston, S., Kitterman, D., Rosenblum, D., Salberg, L., et al. (2014). Corrigendum to "observational study of contracts processing at 29 CTSA sites". *Clinical and Translational Science, 7*(4), 348-348.

Kiss, G., & Van Santen, J. P. H. (2013). Estimating speaker-specific intonation patterns using the linear alignment model. *14th Annual Conference of the International Speech Communication*

Association, INTERSPEECH 2013, Lyon. pp. 354-358.

Modeling speaker-specific intonation is important in several areas, including speaker identification, verification, and imitation using text-to-speech synthesis. However the choice of the intonation model and the estimation of its parameters from spontaneous speech remains a challenge. We propose a way to estimate speaker-specific intonation parameters for a particular superpositional model, the Simplified Linear Alignment Model [1], using robust per-utterance and overall statistics of spontaneous speech. We used this method to compare the intonation of children with autism or language impairment, who often have atypical speech prosody, with that of typically developing children. We found significant differences between the groups, which demonstrates the effectiveness of the proposed method. Copyright © 2013 ISCA.

Koenig, L., Dall, T. M., Ruiz Jr., D., Saavoss, J., & Tongue, J. (2014). Can value-based insurance impose societal costs? *Value in Health,*

Background: Among policy alternatives considered to reduce health care costs and improve outcomes, value-based insurance design (VBID) has emerged as a promising option. Most applications of VBID, however, have not used higher cost sharing to discourage specific services. In April 2011, the state of Oregon introduced a policy for public employees that required additional cost sharing for high-cost procedures such as total knee arthroplasty (TKA). Objectives: Our objectives were to estimate the societal impact of higher co-pays for TKA using Oregon as a case study and building on recent work demonstrating the effects of knee osteoarthritis and surgical treatment on employment and disability outcomes. Methods: We used a Markov model to estimate the societal impact in terms of quality of life, direct costs, and indirect costs of higher co-pays for TKA using Oregon as a case study. Results: We found that TKA for a working population can generate societal benefits that offset the direct medical costs of the procedure. Delay in receiving surgical care, because of higher co-payment or other reasons, reduced the societal savings from TKA. Conclusions: We conclude that payers moving toward value-based cost sharing should consider consequences beyond direct medical expenses. © 2014 International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Kruse, L. C., Walter, N. A., & Buck, K. J. (2014). Mpdz expression in the caudolateral substantia nigra pars reticulata is crucially involved in alcohol withdrawal. *Genes, Brain, and Behavior,*

Association studies implicate the multiple PDZ domain protein (MUPP1/MPDZ) gene in risk for alcoholism in humans and alcohol withdrawal in mice. Although manipulation of the Mpdz gene by homologous recombination and bacterial artificial chromosome transgenesis has suggested that its expression affects alcohol withdrawal risk, the potential confounding effects of linked genes and developmental compensation currently limit interpretation. Here, using RNA interference, we directly test the impact of Mpdz expression on alcohol withdrawal severity and provide brain regional mechanistic information. Lentiviral-mediated delivery of Mpdz short hairpin RNA (shRNA) to the caudolateral substantia nigra pars reticulata significantly reduces Mpdz expression and exacerbates alcohol withdrawal convulsions compared to control mice delivered a scrambled shRNA. Neither baseline nor pentylenetetrazol enhanced convulsions differed between Mpdz shRNA and control animals, indicating that Mpdz expression in the caudolateral substantia nigra pars reticulata does not generally affect seizure susceptibility. To our knowledge, these represent the first in vivo Mpdz RNA interference analyses, and provide the first direct evidence that Mpdz expression impacts behavior. Our results confirm that Mpdz is a quantitative trait gene for alcohol withdrawal and demonstrate that its expression in the caudolateral substantia nigra pars reticulata is crucially involved in risk for alcohol withdrawal.

Kubicky, C. D., Sahgal, A., Chang, E. L., & Lo, S. S. (2014). Rare primary central nervous system tumors. *Rare Tumors, 6*(3), 105-110.

An estimated 69,720 new cases of primary central nervous system tumors are expected to be diagnosed in 2013 based on projection using the 2013 Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report (www.cbtrus.org). Meningiomas, gliomas, nerve sheath tumors, and pituitary tumors together constitute more than 85% of all primary central nervous system tumors diagnosed in the US. There are some tumors which constitute less than 1% of all brain tumors. The purpose of this paper is to provide an overview of the clinical, pathologic and therapeutic aspects of some of the more commonly encountered rare primary brain tumors, including atypical teratoid/rhabdoid tumor, choroid plexus carcinoma, ganglioglioma, hemangiopericytoma, and pleomorphic xanthoastrocytoma. & copy; C.D. Kubicky et al., 2014.

Kudenchuk, P. J., Brown, S. P., Daya, M., Morrison, L. J., Powell, J., Leroux, B., et al. (2014). Regarding manuscript: "resuscitation outcomes consortium-amiodarone, lidocaine, or placebo study: Rationale and methodology behind out-of-hospital cardiac arrest antiarrhythmic drug trial". *American Heart Journal,*

Kun, A. L., Palinko, O., Medenica, Z., & Heeman, P. A. (2013). On the feasibility of using pupil diameter to estimate cognitive load changes for in-vehicle spoken dialogues. *14th Annual Conference of the International Speech Communication Association, INTERSPEECH 2013,* Lyon. pp. 3766-3770.

In a driving simulator study, we explore the feasibility of using pupil diameter to estimate how the cognitive load of the driver changes during a spoken dialogue with a remote conversant. We confirm that it is feasible to use pupil diameter to differentiate between parts of the dialogue that increase the cognitive load of the driver, and those that decrease it. Our long term goal is to build a spoken dialogue system that can adapt its behavior when the driver is under high cognitive load, whether from the driving task or the dialogue task. Copyright © 2013 ISCA.

L'Abbate, A., Macchia, G., D'Addabbo, P., Lonoce, A., Tolomeo, D., Trombetta, D., et al. (2014). Genomic organization and evolution of double minutes/homogeneously staining regions with MYC amplification in human cancer. *Nucleic Acids Research, 42*(14), 9131-9145.

The mechanism for generating double minutes chromosomes (dmin) and homogeneously staining regions (hsr) in cancer is still poorly understood. Through an integrated approach combining nextgeneration sequencing, single nucleotide polymorphism array, fluorescent in situ hybridization and polymerase chain reaction-based techniques, we inferred the fine structure ofMYC-containing dmin/hsr amplicons harboring sequences from several different chromosomes in seven tumor cell lines, and characterized an unprecedented number of hsr insertion sites. Local chromosome shattering involving a single-step catastrophic event (chromothripsis) was recently proposed to explain clustered chromosomal rearrangements and genomic amplifications in cancer. Our bioinformatics analyses based on the listed criteria to define chromothripsis led us to exclude it as the driving force underlying amplicon genesis in our samples. Instead, the finding of coexisting heterogeneous amplicons, differing in their complexity and chromosome content, in

cell lines derived from the same tumor indicated the occurrence of a multistep evolutionary process in the genesis of dmin/hsr. Our integrated approach allowed us to gather a complete view of the complex chromosome rearrangements occurring within MYC amplicons, suggesting that more than one model may be invoked to explain the origin of dmin/hsr in cancer. Finally, we identified PVT1 as a target of fusion events, confirming its role as breakpoint hotspot in MYC amplification.

Langarani, M. S. E., Klabbers, E., & Van Santen, J. (2014). A novel pitch decomposition method for the generalized linear alignment model. *2014 IEEE International Conference on Acoustics, Speech, and Signal Processing, ICASSP 2014,* Florence. pp. 2584-2588.

Superpositional models of intonation typically propose decomposing fundamental frequency (F0) contours into phrase curves and accent curves, aligned with phrases and left-headed feet, respectively. Extracting these component curves from F0 contours without making undue assumptions is challenging. We propose a novel method for decomposing pitch curves, based on the assumption that accent curves can be described by combining skewed normal distributions and sigmoid functions. In contrast to an earlier pitch decomposition algorithm ('PRISM'), this allows for simple joint optimization of phrase and accent curve parameters, using fewer parameters. The proposed method was evaluated on three speech corpora containing: (1) synthetically generated pitch curves, (2) all-sonorant utterances, and (3) utterances containing both sonorant and non-sonorant speech sounds. The root weighted mean squared error is small, and, on the corpus for which comparable data are available, is significantly smaller than for PRISM.

Lechowicz, M. J., Lazarus, H. M., Carreras, J., Laport, G. G., Cutler, C. S., Wiernik, P. H., et al. (2014). Allogeneic hematopoietic cell transplantation for mycosis fungoides and sezary syndrome. *Bone Marrow Transplantation,*

We describe outcomes after allogeneic hematopoietic cell transplantation (HCT) for mycosis fungoides and Sezary syndrome (MF/SS). Outcomes of 129 subjects with MF/SS reported to the Center for the International Blood and Marrow Transplant from 2000-2009. Median time from

diagnosis to transplant was 30 (4-206) months and most subjects were with multiply relapsed/ refractory disease. The majority (64%) received non-myeloablative conditioning (NST) or reduced intensity conditioning (RIC). NST/RIC recipients were older in age compared with myeloablative recipients (median age 51 vs 44 years, P=0.005) and transplanted in recent years. Non-relapse mortality (NRM) at 1 and 5 years was 19% (95% confidence interval (CI) 12-27%) and 22% (95% CI 15-31%), respectively. Risk of disease progression was 50% (95% CI 41-60%) at 1 year and 61% (95% CI 50-71%) at 5 years. PFS at 1 and 5 years was 31% (95% CI 22-40%) and 17% (95% CI 9-26%), respectively. OS at 1 and 5 years was 54% (95% CI 45-63%) and 32% (95% CI 22-44%), respectively. Allogeneic HCT in MF/SS results in 5-year survival in approximately one-third of patients and of those, half remain disease-free.Bone Marrow Transplantation advance online publication, 28 July 2014; doi:10.1038/bmt.2014.161.

Lee, C. S., Mudd, J. O., Gelow, J. M., Nguyen, T., Hiatt, S. O., Green, J. K., et al. (2014). Background and design of the profiling biobehavioral responses to mechanical support in advanced heart failure study. *Journal of Cardiovascular Nursing, 29*(5), 405-415.

Background: Unexplained heterogeneity in response to ventricular assist device (VAD) implantation for the management of advanced heart failure impedes our ability to predict favorable outcomes, provide adequate patient and family education, and personalize monitoring and symptom management strategies. The purpose of this article was to describe the background and the design of a study entitled "Profiling Biobehavioral Responses to Mechanical Support in Advanced Heart Failure" (PREMISE). Study Design and Methods: PREMISE is a prospective cohort study designed to (1) identify common and distinct trajectories of change in physical and psychological symptom burden; (2) characterize common trajectories of change in serum biomarkers of myocardial stress, systemic inflammation, and endothelial dysfunction; and (3) quantify associations between symptoms and biomarkers of pathogenesis in adults undergoing VAD implantation. Latent growth mixture modeling, including parallel process and cross-classification modeling, will be used to address the study aims and will entail identifying trajectories, quantifying associations between trajectories and both clinical and quality-of-life outcomes, and identifying predictors of favorable symptom and biomarker responses to VAD implantation. Conclusions: Research findings from the PREMISE study will be used to enhance

shared patient and provider decision making and to shape a much-needed new breed of interventions and clinical management strategies that are tailored to differential symptom and pathogenic responses to VAD implantation.

Lee, J. J., Protheroe, C. A., Luo, H., Ochkur, S. I., Scott, G. D., Zellner, K. R., et al. (2014). Eosinophil-dependent skin innervation and itching following contact toxicant exposure in mice. *The Journal of Allergy and Clinical Immunology,*

BACKGROUND: Contact toxicant reactions are accompanied by localized skin inflammation and concomitant increases in site-specific itch responses. The role(s) of eosinophils in these reactions is poorly understood. However, previous studies have suggested that localized eosinophil-nerve interactions at sites of inflammation significantly alter tissue innervation. OBJECTIVE: To define a potential mechanistic link between eosinophils and neurosensory responses in the skin leading to itching. METHODS: BALB/cJ mice were exposed to different contact toxicants, identifying trimellitic anhydride (TMA) for further study on the basis of inducing a robust eosinophilia accompanied by degranulation. Subsequent studies using TMA were performed with wild type versus eosinophil-deficient PHIL mice, assessing edematous responses and remodeling events such as sensory nerve innervation of the skin and induced pathophysiological responses (ie, itching). RESULTS: Exposure to TMA, but not dinitrofluorobenzene, resulted in a robust eosinophil skin infiltrate accompanied by significant levels of degranulation. Follow-up studies using TMA with wild type versus eosinophil-deficient PHIL mice showed that the induced edematous responses and histopathology were, in part, causatively linked with the presence of eosinophils. Significantly, these data also demonstrated that eosinophil-mediated events correlated with a significant increase in substance P content of the cutaneous nerves and an accompanying increase in itching, both of which were abolished in the absence of eosinophils. CONCLUSIONS: Eosinophil-mediated events following TMA contact toxicant reactions increase skin sensory nerve substance P and, in turn, increase itching responses. Thus, eosinophil-nerve interactions provide a potential mechanistic link between eosinophil-mediated events and neurosensory responses following exposure to some contact toxicants.

Lee, Y., Liu, L., & Pu, C. (1997). Towards interoperable heterogeneous information systems: An experiment using the DIOM approach. *1997 ACM Symposium on Applied Computing, SAC 1997,* San Jose, CA. pp. 112-114.

The Distributed Interoperable Object Model (DIOM) [5] introduced the approach that explicitly defines the interfaces of an information consumer and an information producer, matching them dynamically to achieve interoperability in heterogeneous information systems with growing number of autonomous data sources as components. In this paper, we describe an experimental implementation of a cooperative information system, built on web browser interfaces, the Oracle database manager, and CGI scripts. This initial implementation demonstrates the practical feasibility of building DIOM-based customizable and scalable solutions for interconnecting information consumers with information producers. Highlights of this simple system include: (1) a demonstration of the DIOM query mediation component with interactive query tracing, (2) a generic wrapper construction library, and (3) a demo accessible over the Internet. © 1997 ACM.

Leung, R. M., Dinnie, K., & Smith, T. L. (2014). When do the risks of repeated courses of corticosteroids exceed the risks of surgery? *International Forum of Allergy and Rhinology,*

Background: The management of chronic rhinosinusitis with nasal polyposis (CRSwNP) becomes unclear when patients require multiple courses of corticosteroids to maintain quality of life. Repeated courses of corticosteroids carry increased risks to patients. Although endoscopic sinus surgery (ESS) is an effective therapeutic modality, it also carries inherent risks. This study aims to identify the threshold at which the risks of repeated courses of corticosteroid exceed the risks of surgery. Methods: An evidence-based risk analysis was simulated using literature-reported complication rates, quality of life changes, and Medicare costs. Simulations were performed from the Medicare patient perspective, societal perspective, and the universal healthcare patient perspective. Results: All 3 simulations demonstrate a breakeven threshold favoring surgery over medical therapy when patients require oral corticosteroids (OCS) more often than once every 2 years in CRSwNP, once per year in CRSwNP/asthma, or twice per year for Samter's triad patients. Conclusion: This represents the first rationalized evidence-based analysis for when surgery should be considered in place of repeated courses of oral corticosteroids. This threshold

provides a guide for otolaryngologists to use when making clinical decisions with patients. © 2014 ARS-AAOA, LLC.

Li, J., Echevarria, K. L., Hughes, D. W., Cadena, J. A., Bowling, J. E., & Lewis II, J. S. (2014). Comparison of cefazolin versus oxacillin for treatment of complicated bacteremia caused by methicillin-susceptible staphylococcus aureus. *Antimicrobial Agents and Chemotherapy, 58*(9), 5117-5124.

Contrary to prior case reports that described occasional clinical failures with cefazolin for methicillin-susceptible Staphylococcus aureus (MSSA) infections, recent studies have demonstrated no difference in outcomes between cefazolin and antistaphylococcal penicillins for the treatment of MSSA bacteremia. While promising, these studies described low frequencies of high-inoculum infections, such as endocarditis. This retrospective study compares clinical outcomes of cefazolin versus oxacillin for complicated MSSA bacteremia at two tertiary care hospitals between January 2008 and June 2012. Fifty-nine patients treated with cefazolin and 34 patients treated with oxacillin were included. Osteoarticular (41%) and endovascular (20%) sources were the predominant sites of infection. The rates of clinical cure at the end of therapy were similar between cefazolin and oxacillin (95% versus 88%; P = 0.25), but overall failure at 90 days was higher in the oxacillin arm (47% versus 24%; P = 0.04). Failures were more likely to have received surgical interventions (63% versus 40%; P = 0.05) and to have an osteoarticular source (57% versus 33%; P = 0.04). Failures also had a longer duration of bacteremia (7 versus 3 days; P = 0.0002), which was the only predictor of failure. Antibiotic selection was not predictive of failure. Rates of adverse drug events were higher in the oxacillin arm (30% versus 3%; P = 0.0006), and oxacillin was more frequently discontinued due to adverse drug events (21% versus 3%; P = 0.01). Cefazolin appears similar to oxacillin for the treatment of complicated MSSA bacteremia but with significantly improved safety. The higher rates of failure with oxacillin may have been confounded by other patient factors and warrant further investigation.

Lieberman, D. (2014). Colon adenoma surveillance: It takes a program. *Gastrointestinal Endoscopy, 80*(3), 479-481.

Lieberman, D. (2014). Colon-polyp surveillance--do patients benefit? *The New England Journal of Medicine, 371*(9), 860-861.

Lin, P., Bach, M., Asquith, M., Lee, A. Y., Akileswaran, L., Stauffer, P., et al. (2014). HLA-B27 and human beta2-microglobulin affect the gut microbiota of transgenic rats. *PloS One, 9*(8), e105684.
The HLA-B27 gene is a major risk factor for clinical diseases including ankylosing spondylitis, acute anterior uveitis, reactive arthritis, and psoriatic arthritis, but its mechanism of risk enhancement is not completely understood. The gut microbiome has recently been shown to influence several HLA-linked diseases. However, the role of HLA-B27 in shaping the gut microbiome has not been previously investigated. In this study, we characterize the differences in the gut microbiota mediated by the presence of the HLA-B27 gene. We identified differences in the cecal microbiota of Lewis rats transgenic for HLA-B27 and human beta2-microglobulin (hbeta2m), compared with wild-type Lewis rats, using biome representational in situ karyotyping (BRISK) and 16S rRNA gene sequencing. 16S sequencing revealed significant differences between transgenic animals and wild type animals by principal coordinates analysis. Further analysis of the data set revealed an increase in Prevotella spp. and a decrease in Rikenellaceae relative abundance in the transgenic animals compared to the wild type animals. By BRISK analysis, species-specific differences included an increase in Bacteroides vulgatus abundance in HLA-B27/hbeta2m and hbeta2m compared to wild type rats. The finding that HLA-B27 is associated with altered cecal microbiota has not been shown before and can potentially provide a better understanding of the clinical diseases associated with this gene.

Linfante, I., Dabus, G., Starosciak, A., Castonguay, A., Gupta, R., Sun, C., et al. (2014). O-032 predictors of poor outcomes despite successful recanalization in patients with acute ischemic stroke. *Journal of Neurointerventional Surgery, 6 Suppl 1*, A17-8.
BACKGROUND: Recanalization of the occluded artery is a powerful predictor of good outcome in acute ischemic stroke secondary to large artery occlusions. Mechanical thrombectomy with stent-trievers results in higher recanalization rates and better outcomes compared to previous devices. However, despite successful recanalization rates (Treatment in Cerebral Infarction, TICI, score >/= 2b) between 70 and 90%, good clinical outcomes assessed by modified Rankin Scale (mRS

>/= 2 is present in 40-50% of patients. We aimed to evaluate predictors of poor outcomes (mRS >/= 2) despite successful recanalization (TICI >/= 2b) in the acute stroke patients treated with the Solitaire device of the North American Solitaire Stent Retriever Acute Stroke (NASA) registry. METHODS: The NASA registry is a multicenter, non-sponsored, physician-conducted, post-marketing registry on the use of SOLITAIRE FR device in 354 acute, large vessels, ischemic stroke patients. Logistic regression was used to evaluate patient characteristics and treatment parameters for association with 90-day mRS score of 0-2 (good outcome) versus 3-6 (poor outcome) within patients who were recanalised successfully (Thrombolysis in Cerebral Infarction or TICI score 2b-3). Univariate tests were followed by development of a multivariable model based on stepwise selection with entry and retention criteria of p /= 2b). Based on 90-day mRS score for 234 of these patients, there were 116 (49.6%) with mRS >/=2. Univariate analysis identified increased risk of mRS >/=2 for each of the following: age >/= 80 years (upper quartile of data), occlusion site other than M1/M2, NIH Stroke Scale (NIHSS) score >/= 18 (median), history of diabetes mellitus (DM), TICI = 2b, use of rescue therapy, not using a balloon-guided catheter (BCG) or intravenous tissue plasminogen activator (IV t-PA), and time to recanalization > 30 min (all p /=80 years, site other than M1/M2, initial NIHSS >/=18, DM, absence of IVtPA, use of rescue therapy and three or more passes were significant independent predictors of poor 90-day outcome in a model with good predictive power (c-index = 0.80). CONCLUSIONS: Age, occlusion site, high NIHSS, diabetes, not receiving IVtPA, use of rescue therapy and three or more passes, were associated with poor 90-day outcome despite successful recanalization. DISCLOSURES: I. Linfante: None. G. Dabus: None. A. Starosciak: None. A. Castonguay: None. R. Gupta: None. C. Sun: None. C. Martin: None. W. Holloway: None. N. Mueller-Kronast: None. J. English: None. T. Malisch: None. F. Marden: None. H. Bozorgchami: None. A. Xavier: None. A. Rai: None. M. Froehler: None. A. Badruddin: None. T. Nguyen: None. M. Taqi: None. M. Abraham: None. V. Janardhan: None. H. Shaltoni: None. R. Novakovic: None. A. Yoo: None. O. Zaidat: None.

Liu, X., & Dawson, D. C. (2014). Cystic fibrosis transmembrane conductance regulator (CFTR) potentiators protect G551D but not DeltaF508 CFTR from thermal instability. *Biochemistry,* The G551D cystic fibrosis transmembrane conductance regulator (CFTR) mutation is associated

with severe disease in approximately 5% of cystic fibrosis patients worldwide. This amino acid substitution in NBD1 results in a CFTR chloride channel characterized by a severe gating defect that can be at least partially overcome in vitro by exposure to a CFTR potentiator. In contrast, the more common DeltaF508 mutation is associated with a severe protein trafficking defect, as well as impaired channel function. Recent clinical trials demonstrated a beneficial effect of the CFTR potentiator, Ivacaftor (VX-770), on lung function of patients bearing at least one copy of G551D CFTR, but no comparable effect on DeltaF508 homozygotes. This difference in efficacy was not surprising in view of the established difference in the molecular phenotypes of the two mutant channels. Recently, however, it was shown that the structural defect introduced by the deletion of F508 is associated with the thermal instability of DeltaF508 CFTR channel function in vitro. This additional mutant phenotype raised the possibility that the differences in the behavior of DeltaF508 and G551D CFTR, as well as the disparate efficacy of Ivacaftor, might be a reflection of the differing thermal stabilities of the two channels at 37 degrees C. We compared the thermal stability of G551D and DeltaF508 CFTR in Xenopus oocytes in the presence and absence of CTFR potentiators. G551D CFTR exhibited a thermal instability that was comparable to that of DeltaF508 CFTR. G551D CFTR, however, was protected from thermal instability by CFTR potentiators, whereas DeltaF508 CFTR was not. These results suggest that the efficacy of VX-770 in patients bearing the G551D mutation is due, at least in part, to the ability of the small molecule to protect the mutant channel from thermal instability at human body temperature.

Loriaux, L. D. (2014). Commentary. *Clinical Chemistry, 60*(8), 1050-1051.

Loriaux, L. D. (2014). Easy bruising in a patient with secondary amenorrhea: Commentary. *Clinical Chemistry, 60*(8), 1050-1051.

Lovejoy, T. I., & Heckman, T. G. (2014). Depression moderates treatment efficacy of an HIV secondary-prevention intervention for HIV-positive late middle-age and older adults. *Behavioral Medicine (Washington, D.C.), 40*(3), 124-133.

An estimated one-third of HIV-positive older adults continues to engage in sexual behaviors that risk HIV transmission or the acquisition of other sexually transmitted infections. A recently completed pilot randomized controlled trial of telephone-administered motivational interviewing

(Tele-MI) targeting sexual risk behavior in 100 HIV-positive late middle-age and older adults found that a four-session Tele-MI intervention reduced episodes of non-condom-protected anal and vaginal intercourse. This secondary analysis examined the moderating effect of baseline depressive symptoms on intervention efficacy. When compared to one session of Tele-MI or standard of care, four sessions of Tele-MI produced greater reductions in sexual risk behavior in participants with subsyndromal depression at baseline but was no more efficacious than the other two conditions for participants with no or elevated baseline depressive symptoms. Large-scale studies that further elucidate the role of depression in sexual risk reduction interventions for HIV-positive persons are needed.

Lowe, J., Erickson, S. J., MacLean, P., Duvall, S. W., Ohls, R. K., & Duncan, A. F. (2014). Associations between maternal scaffolding and executive functioning in 3 and 4year olds born very low birth weight and normal birth weight. *Early Human Development, 90*(10), 587-593.
BACKGROUND: Deficits in executive function, including measures of working memory, inhibition and cognitive flexibility, have been documented in preschoolers born very low birth weight (VLBW) compared with preschoolers born normal birth weight (NBW). Maternal verbal scaffolding has been associated with positive outcomes for both at-risk and typically developing preschoolers. AIMS: The purpose of this study was to examine associations between maternal verbal scaffolding, Verbal IQ (VIQ) and executive function measures in preschoolers born VLBW. SUBJECTS: A total of 64 VLBW and 40 NBW preschoolers ranging in age from 3 (1/2) to 4years participated in the study. OUTCOME MEASURES: VIQ was measured with the Wechsler Preschool and Primary Scale of Intelligence - Third Edition. Executive function tests included the Bear Dragon, Gift Delay Peek, Reverse Categorization and Dimensional Change Card Sort-Separated Dimensions. STUDY DESIGN: Maternal verbal scaffolding was coded during a videotaped play session. Associations between maternal verbal scaffolding and preschoolers' measures of VIQ and executive function were compared. Covariates included test age, maternal education, and gender. RESULTS: Preschoolers born VLBW performed significantly worse on VIQ and all executive function measures compared to those born NBW. Maternal verbal scaffolding was associated with VIQ for VLBW preschoolers and Gift Delay Peek for the NBW group. Girls born VLBW outperformed boys born VLBW on VIQ and Bear Dragon. CONCLUSION: Integrating

scaffolding skills training as part of parent-focused intervention may be both feasible and valuable for early verbal reasoning and EF development.

Lynch, M. M., & Roecker, J. (2007). *Project managing e-learning: A handbook for successful design, delivery and management* Routledge.

Project Managing E-learning provides an essential framework, based on the globally accepted IPECC model, for planning, designing, delivering, managing and evaluating e-learning projects successfully. It focuses on practical, easy-to-understand methods and offers applications of project management principles in the real world. Illustrated by case studies of projects undertaken in business and academia it provides a step-by-step guide and highlights where projects typically fail. Each chapter begins with a definition and conceptualisation of the process, provides examples of how the process steps may vary dependent on organization or project size and discusses the typical problems organisations face when performing steps in the project management process. Covering all of the essentials as well as cutting-edge technology, it guides designers and managers through all stages of implementing and managing a project. Selected themes include: using focus groups. gaining sponsors. risk management. pedagogical considerations. testing. quality control. how to know when trouble is imminent. PM software systems. podcasting. The practical framework and sound advice offered in Project Managing E-learning is essential reading for all those who want to successfully implement and manage high quality e-learning in both academic and corporate training settings on time and to budget. © 2007 Maggie McVay Lynch and John Roecker. All rights reserved.

Lyon, E., Schrijver, I., Weck, K. E., Ferreira-Gonzalez, A., Richards, C. S., & Palomaki, G. E. (2014). Molecular genetic testing for cystic fibrosis: Laboratory performance on the college of american pathologists external proficiency surveys. *Genetics in Medicine : Official Journal of the American College of Medical Genetics,*

Background:Molecular testing for cystic fibrosis mutations is widespread and routine in reproductive decision making and diagnosis. Our objective was to assess the level of performance of laboratories for this test.Methods:The College of American Pathologists administers external proficiency testing with multiple DNA samples distributed biannually. Results are analyzed,

reviewed, and graded by the joint College of American Pathologists/American College of Medical Genetics and Genomics Biochemical and Molecular Genetics Committee. Assessment is based on genotype and associated clinical interpretation.Results:Overall, 357 clinical laboratories participated in the proficiency testing survey between 2003 and 2013 (322 in the United States and 35 international). In 2013, US participants reported performing nearly 120,000 tests monthly. Analytical sensitivity and specificity of US laboratories were 98.8% (95% confidence interval: 98.4-99.1%) and 99.6% (95% confidence interval: 99.4-99.7%), respectively. Analytical sensitivity improved between 2003 and 2008 (from 97.9 to 99.3%; P = 0.007) and remained steady thereafter. Clinical interpretation matched the intended response for 98.8, 86.0, and 91.0% of challenges with no, one, or two mutations, respectively. International laboratories performed similarly.Discussion:Laboratory testing for cystic fibrosis in the United States has improved since 2003, and these data demonstrate a high level of quality. Neither the number of samples tested nor test methodology affected performance.Genet Med advance online publication 31 July 2014Genetics in Medicine (2014); doi:10.1038/gim.2014.93.

Macmillan, H., Strohman, M. J., Ayyangar, S., Jiang, W., Rajasekaran, N., Spura, A., et al. (2014). The MHC class II cofactor HLA-DM interacts with ig in B cells. *Journal of Immunology (Baltimore, Md.: 1950),*

B cells internalize extracellular Ag into endosomes using the Ig component of the BCR. In endosomes, Ag-derived peptides are loaded onto MHC class II proteins. How these pathways intersect remains unclear. We find that HLA-DM (DM), a catalyst for MHC class II peptide loading, coprecipitates with Ig in lysates from human tonsillar B cells and B cell lines. The molecules in the Ig/DM complexes have mature glycans, and the complexes colocalize with endosomal markers in intact cells. A larger fraction of Ig precipitates with DM after BCR crosslinking, implying that complexes can form when DM meets endocytosed Ig. In vitro, in the endosomal pH range, soluble DM directly binds the Ig Fab domain and increases levels of free Ag released from immune complexes. Taken together, these results argue that DM and Ig intersect in the endocytic pathway of B cells with potential functional consequences.

Maeda, R., Kindt, K. S., Mo, W., Morgan, C. P., Erickson, T., Zhao, H., et al. (2014). Tip-link protein protocadherin 15 interacts with transmembrane channel-like proteins TMC1 and TMC2. *Proceedings of the National Academy of Sciences of the United States of America,*

The tip link protein protocadherin 15 (PCDH15) is a central component of the mechanotransduction complex in auditory and vestibular hair cells. PCDH15 is hypothesized to relay external forces to the mechanically gated channel located near its cytoplasmic C terminus. How PCDH15 is coupled to the transduction machinery is not clear. Using a membrane-based two-hybrid screen to identify proteins that bind to PCDH15, we detected an interaction between zebrafish Pcdh15a and an N-terminal fragment of transmembrane channel-like 2a (Tmc2a). Tmc2a is an ortholog of mammalian TMC2, which along with TMC1 has been implicated in mechanotransduction in mammalian hair cells. Using the above-mentioned two-hybrid assay, we found that zebrafish Tmc1 and Tmc2a can interact with the CD1 or CD3 cytoplasmic domain isoforms of Pcdh15a, and this interaction depends on the common region shared between the two Pcdh15 isoforms. Moreover, an interaction between mouse PCDH15-CD3 and TMC1 or TMC2 was observed in both yeast two-hybrid assays and coimmunoprecipitation experiments. To determine whether the Pcdh15-Tmc interaction is relevant to mechanotransduction in vivo, we overexpressed N-terminal fragments of Tmc2a in zebrafish hair cells. Overexpression of the Tmc2a N terminus results in mislocalization of Pcdh15a within hair bundles, together with a significant decrease in mechanosensitive responses, suggesting that a Pcdh15a-Tmc complex is critical for mechanotransduction. Together, these results identify an evolutionarily conserved association between the fish and mouse orthologs of PCDH15 and TMC1 and TMC2, supporting the notion that TMCs are key components of the transduction complex in hair cells.

Malhotra, R., Turner, K., Sonnenberg, A., & Genta, R. M. (2014). High prevalence of inflammatory bowel disease in united states residents of indian ancestry. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association,*

BACKGROUND & AIMS: It is unclear whether the reported low prevalence of inflammatory bowel disease (IBD) in Southern and Eastern Asia is real (caused by genetic or environmental factors) or spurious (because of differences in awareness of the condition among physicians or different interpretations of endoscopic and histologic features). We aimed to estimate the prevalence of

IBD in patients of different ethnicities who underwent endoscopy in the United States, with ileocolonic biopsies evaluated by a single group of gastrointestinal pathologists. METHODS: We used a national pathology database to collect data on 1,027,977 subjects who underwent colonoscopy with ileocolonic biopsies from January 2008 through December 2013 throughout the United States; mucosal biopsy specimens were evaluated and reported by 1 group of 35 histopathologists. Patients were stratified into the following ancestries: Indian (persons with ancestry in the Indian subcontinent), East Asian (China, Korea, Japan, and Vietnam), Hispanic, Jewish, and other. The prevalence of ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis was determined for each ethnic group. RESULTS: In the study population, 30,812 patients were diagnosed with IBD (20,308 with UC, 7706 with CD, and 2798 with indeterminate colitis). UC was more commonly associated with Indian and Jewish ethnicity and less commonly associated with East Asian and Hispanic ethnicity. Similar patterns also applied to CD and to all types of IBD analyzed jointly. Among Indian patients, 11.7% of those of Gujarati origins had IBD, compared with 7.9% of other Indians (odds ratio, 1.5; 95% confidence interval, 1.14-2.11). CONCLUSIONS: Patients of Indian origin living in the United States have a greater risk for all types of IBD than other American populations. East Asians and Hispanics have a lower risk, possibly similar to that of the populations still living in their original countries. These findings may have relevance to the practice of gastroenterology in countries where there are sizable portions of the population with roots in the Indian subcontinent.

Malinoski, D. (2014). How to help hispanic families benefit from organ donation after a tragedy. *JAMA Surgery,*

Marhenke, S., Buitrago-Molina, L. E., Endig, J., Orlik, J., Schweitzer, N., Klett, S., et al. (2014). P21 promotes sustained liver regeneration and hepatocarcinogenesis in chronic cholestatic liver injury. *Gut, 63*(9), 1501-1512.

Background and aims The cyclin-dependent kinase inhibitor p21 has been implicated as a tumour suppressor. Moreover, recent genetic studies suggest that p21 might be a potential therapeutic target to improve regeneration in chronic diseases. The aim of this study was to delineate the role of p21 in chronic liver injury and to specify its role in hepatocarcinogenesis in a mouse model

of chronic cholestatic liver injury. Methods: The degree of liver injury, regeneration and tumour formation was assessed in Mdr2-/-mice and compared with Mdr2/p21-/- mice. Moreover, the role of p21 was evaluated in hepatoma cells in vitro and in human hepatocellular carcinoma (HCC). Results: Mdr2-/-mice developed HCCs as a consequence of chronic inflammatory liver injury. In contrast, tumour development was profoundly delayed in Mdr2/p21 -/- mice. Delayed tumour development was accompanied by markedly impaired liver regeneration in Mdr2/p21-/- mice. Moreover, the regenerative capacity of the Mdr2/p21-/- livers in response to partial hepatectomy declined with age in these mice. Hepatocyte transplantation experiments revealed that impaired liver regeneration was due to intrinsic factors within the cells and changes in the Mdr2/p21-/- microenvironment. In human HCCs, a subset of tumours expressed p21, which was associated with a significant shorter patient survival. Conclusions: We provide experimental evidence that p21 is required for sustained liver regeneration and tumour development in chronic liver injury indicating that p21 needs to be tightly regulated in order to balance liver regeneration and cancer risk. Moreover, we identify p21 as a negative prognostic marker in human HCC.

Marrero, J. A., Ahn, J., & Rajender Reddy, K. (2014). ACG clinical guideline: The diagnosis and management of focal liver lesions. *The American Journal of Gastroenterology,*

Focal liver lesions (FLL) have been a common reason for consultation faced by gastroenterologists and hepatologists. The increasing and widespread use of imaging studies has led to an increase in detection of incidental FLL. It is important to consider not only malignant liver lesions, but also benign solid and cystic liver lesions such as hemangioma, focal nodular hyperplasia, hepatocellular adenoma, and hepatic cysts, in the differential diagnosis. In this ACG practice guideline, the authors provide an evidence-based approach to the diagnosis and management of FLL.Am J Gastroenterol advance online publication, 19 August 2014; doi:10.1038/ajg.2014.213.

Mathiasen, S., Christensen, S. M., Fung, J. J., Rasmussen, S. G., Fay, J. F., Jorgensen, S. K., et al. (2014). Nanoscale high-content analysis using compositional heterogeneities of single proteoliposomes. *Nature Methods, 11*(9), 931-934.

Proteoliposome reconstitution is a standard method to stabilize purified transmembrane proteins

in membranes for structural and functional assays. Here we quantified intrareconstitution heterogeneities in single proteoliposomes using fluorescence microscopy. Our results suggest that compositional heterogeneities can severely skew ensemble-average proteoliposome measurements but also enable ultraminiaturized high-content screens. We took advantage of this screening capability to map the oligomerization energy of the beta2-adrenergic receptor using approximately 10(9)-fold less protein than conventional assays.

Matijevic, N., Wang, Y. W., Wade, C. E., Holcomb, J. B., Cotton, B. A., Schreiber, M. A., et al. (2014). Cellular microparticle and thrombogram phenotypes in the prospective observational multicenter major trauma transfusion (PROMMTT) study: Correlation with coagulopathy. *Thrombosis Research, 134*(3), 652-658.

BACKGROUND: Trauma-induced coagulopathy following severe injury is associated with increased bleeding and mortality. Injury may result in alteration of cellular phenotypes and release of cell-derived microparticles (MP). Circulating MPs are procoagulant and support thrombin generation (TG) and clotting. We evaluated MP and TG phenotypes in severely injured patients at admission, in relation to coagulopathy and bleeding. METHODS: As part of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study, research blood samples were obtained from 180 trauma patients requiring transfusions at 5 participating centers. Twenty five healthy controls and 40 minimally injured patients were analyzed for comparisons. Laboratory criteria for coagulopathy was activated partial thromboplastin time (APTT) >/=35sec. Samples were analyzed by Calibrated Automated Thrombogram to assess TG, and by flow cytometry for MP phenotypes [platelet (PMP), erythrocyte (RMP), leukocyte (LMP), endothelial (EMP), tissue factor (TFMP), and Annexin V positive (AVMP)]. RESULTS: 21.7% of patients were coagulopathic with the median (IQR) APTT of 44sec (37, 53), and an Injury Severity Score of 26 (17, 35). Compared to controls, patients had elevated EMP, RMP, LMP, and TFMP (all $p<0.001$), and enhanced TG ($p<0.0001$). However, coagulopathic PROMMTT patients had significantly lower PMP, TFMP, and TG, higher substantial bleeding, and higher mortality compared to non-coagulopathic patients (all $p<0.001$). CONCLUSIONS: Cellular activation and enhanced TG are predominant after trauma and independent of injury severity. Coagulopathy was associated with lower thrombin peak and

rate compared to non-coagulopathic patients, while lower levels of TF-bearing PMPs were associated with substantial bleeding.

Matsumura, H., Umezawa, K., Takeda, K., Sugimoto, N., Ishida, T., Samejima, M., et al. (2014). Discovery of a eukaryotic pyrroloquinoline quinone-dependent oxidoreductase belonging to a new auxiliary activity family in the database of carbohydrate-active enzymes. *Plos One, 9*(8) Pyrroloquinoline quinone (PQQ) is a redox cofactor utilized by a number of prokaryotic dehydrogenases. Not all prokaryotic organisms are capable of synthesizing PQQ, even though it plays important roles in the growth and development of many organisms, including humans. The existence of PQQ-dependent enzymes in eukaryotes has been suggested based on homology studies or the presence of PQQ-binding motifs, but there has been no evidence that such enzymes utilize PQQ as a redox cofactor. However, during our studies of hemoproteins, we fortuitously discovered a novel PQQ-dependent sugar oxidoreductase in a mushroom, the basidiomycete Coprinopsis cinerea. The enzyme protein has a signal peptide for extracellular secretion and a domain for adsorption on cellulose, in addition to the PQQ-dependent sugar dehydrogenase and cytochrome domains. Although this enzyme shows low amino acid sequence homology with known PQQ-dependent enzymes, it strongly binds PQQ and shows PQQ-dependent activity. BLAST search uncovered the existence of many genes encoding homologous proteins in bacteria, archaea, amoebozoa, and fungi, and phylogenetic analysis suggested that these quinoproteins may be members of a new family that is widely distributed not only in prokaryotes, but also in eukaryotes. © 2014 Matsumura et al.

Matthews, M., Nigg, J. T., & Fair, D. A. (2014). Attention deficit hyperactivity disorder. *Current Topics in Behavioral Neurosciences, 16*, 235-266.

Over the last two decades, there have been numerous technical and methodological advances available to clinicians and researchers to better understand attention deficit hyperactivity disorder (ADHD) and its etiology. Despite the growing body of literature investigating the disorder's pathophysiology, ADHD remains a complex psychiatric disorder to characterize. This chapter will briefly review the literature on ADHD, with a focus on its history, the current genetic insights, neurophysiologic theories, and the use of neuroimaging to further understand the etiology. We

address some of the major concerns that remain unclear about ADHD, including subtype instability, heterogeneity, and the underlying neural correlates that define the disorder. We highlight that the field of ADHD is rapidly evolving; the descriptions provided here will hopefully provide a sturdy foundation for which to build and improve our understanding of the disorder.

McCarty, D., Bovett, R., Burns, T., Cushing, J., Glynn, M. E., Kruse, S. J., et al. (2014). Oregon's strategy to confront prescription opioid misuse: A case study. *Journal of Substance Abuse Treatment,*

Governor John Kitzhaber appointed a Prescription Drug Taskforce to address Oregon's opioid epidemic. This case study reviews the Taskforce's participation in the National Governors Association State Policy Academy on Reducing Prescription Drug Abuse. To address the challenge of the misuse and abuse of prescription opioids, the Taskforce developed a strategy for practice change, community education and enhanced access to safe opioid disposal using stakeholder meetings, consensus development, and five action steps: (1) fewer pills in circulation, (2) educate prescribers and the public on the risks of opioid use, (3) foster safe disposal of unused medication, (4) provide treatment for opioid dependence, and (5) continued leadership from the Governor, health plans and health professionals. Although the story is ongoing, there are lessons for leadership in other states and for public health and medical practitioners throughout the country. © 2014.

McDaniel, A. S., Zhai, Y., Cho, K. R., Dhanasekaran, S. M., Montgomery, J. S., Palapattu, G., et al. (2014). HRAS mutations are frequent in inverted urothelial neoplasms. *Human Pathology, 45*(9), 1957-1965.

Inverted urothelial papilloma (IUP) is an uncommon neoplasm of the urinary bladder with distinct morphologic features. Studies regarding the role of human papillomavirus (HPV) in the etiology of IUP have provided conflicting evidence of HPV infection. In addition, little is known regarding the molecular alterations present in IUP or other urothelial neoplasms, which might demonstrate inverted growth pattern like low-grade or high-grade urothelial carcinoma (UCA). Here, we evaluated for the presence of common driving somatic mutations and HPV within a cohort of IUPs, (n = 7) noninvasive low-grade papillary UCAs with inverted growth pattern (n = 5), and

noninvasive high-grade papillary UCAs with inverted growth pattern (n = 8). HPV was not detected in any case of IUP or inverted UCA by either in situ hybridization or by polymerase chain reaction. Next-generation sequencing identified recurrent mutations in HRAS (Q61R) in 3 of 5 IUPs, described for the first time in this neoplasm. Additional mutations of Ras pathway members were detected including HRAS, KRAS, and BRAF. The presence of Ras pathway member mutations at a relatively high rate suggests this pathway may contribute to pathogenesis of inverted urothelial neoplasms. In addition, we did not find any evidence supporting a role for HPV in the etiology of IUP.

McFarlane, W. R., Levin, B., Travis, L., Lucas, F. L., Lynch, S., Verdi, M., et al. (2014). Clinical and functional outcomes after 2 years in the early detection and intervention for the prevention of psychosis multisite effectiveness trial. *Schizophrenia Bulletin,*

Objective: To test effectiveness of the Early Detection, Intervention, and Prevention of Psychosis Program in preventing the onset of severe psychosis and improving functioning in a national sample of at-risk youth. Methods: In a risk-based allocation study design, 337 youth (age 12-25) at risk of psychosis were assigned to treatment groups based on severity of positive symptoms. Those at clinically higher risk (CHR) or having an early first episode of psychosis (EFEP) were assigned to receive Family-aided Assertive Community Treatment (FACT); those at clinically lower risk (CLR) were assigned to receive community care. Between-groups differences on outcome variables were adjusted statistically according to regression-discontinuity procedures and evaluated using the Global Test Procedure that combined all symptom and functional measures. Results: A total of 337 young people (mean age: 16.6) were assigned to the treatment group (CHR + EFEP, n = 250) or comparison group (CLR, n = 87). On the primary variable, positive symptoms, after 2 years FACT, were superior to community care (2 df, $p < .0001$) for both CHR ($p = .0034$) and EFEP ($p < .0001$) subgroups. Rates of conversion (6.3% CHR vs 2.3% CLR) and first negative event (25% CHR vs 22% CLR) were low but did not differ. FACT was superior in the Global Test ($p = .0007$; $p = .024$ for CHR and $p = .0002$ for EFEP, vs CLR) and in improvement in participation in work and school ($p = .025$). Conclusion: FACT is effective in improving positive, negative, disorganized and general symptoms, Global Assessment

of Functioning, work and school participation and global outcome in youth at risk for, or experiencing very early, psychosis.

McKenna, D. T., & Mattar, S. G. (2014). *What is wrong with the training of general surgery?* Academic Press Inc.

McMillan, G. P., Thielman, E. J., Wypych, K., & Henry, J. A. (2014). A bayesian perspective on tinnitus pitch matching. *Ear and Hearing,*

OBJECTIVES:: New tinnitus therapies are being developed and marketed that target the patient's tinnitus frequency. This frequency is estimated clinically by pitch matching, which has the patient identify the pure tone that is closest to the perceived tinnitus frequency. Though widely used, pitch matching is heavily criticized as unreliable, and the degree of reliability varies among patients. At the very least, it is recommended that multiple pitch matches be used to identify the patient's tinnitus frequency. Even so, it is not clear how many pitch matches to collect, how they should be combined, or how doing so will enhance the audiologist's certainty about the true tinnitus frequency. In this article, we describe a simple Bayesian method of sequentially combining pitch matches until acceptable precision is achieved and illustrate the method in 10 patients with chronic tinnitus. DESIGN:: Subjects were recruited from previous study participants and support group attendees at the National Center for Rehabilitative Auditory Research. Thirty tinnitus pitch matches were elicited from 10 patients with chronic, monotonal tinnitus. RESULTS:: A Bayesian sequential analysis yielded estimated tinnitus frequencies for 7 patients that were within one-quarter octave of their true value with 90% certainty. Between four and twenty pitch matches were required to achieve acceptable results in these seven patients. CONCLUSIONS:: Despite criticism, pitch matching is widely used to estimate tinnitus frequency. We address reliability concerns with a Bayesian sequential analysis to jointly estimate tinnitus frequency and reliability. The method is easily applied.

McMillan, K. K., Pugh, M. J., Hamid, H., Salinsky, M., Pugh, J., Noel, P. H., et al. (2014). Providers' perspectives on treating psychogenic nonepileptic seizures: Frustration and hope. *Epilepsy & Behavior : E&B, 37C*, 276-281.

Recent diagnostic and treatment advances in psychogenic nonepileptic seizures (PNES) have the

potential to improve care for patients, but little is known about the current state of PNES care delivery in the Veterans Health Administration (VA). We conducted semistructured interviews with 74 health-care clinicians and workers in the VA, eliciting provider perceptions of PNES care. Data were analyzed according to principles of Grounded Theory. The results revealed variation in care and two emergent domain themes of frustration and hope. Frustration was manifest in subthemes including Complexity, Patient Acceptance, Uncertainty About Treatment, Need for Evidence-based Treatment, and Failure of Cross-Disciplinary Collaboration between neurologists and mental health providers. Hope encompassed subthemes of Positive Attitudes, Developing Cross-Disciplinary Treatment, and Specific PNES Care. Increased resources for diagnosing, treating, and researching PNES have improved awareness of the disorder. More research is needed to understand patients' and caregivers' perceptions of PNES care.

Mendez, G., Ozpinar, A., Raskin, J., Gultekin, S. H., & Ross, D. A. (2014). Case comparison and literature review of glioblastoma: A tale of two tumors. *Surgical Neurology International, 5*, 121-7806.138034. eCollection 2014.

BACKGROUND: Diagnosis of glioblastoma multiforme (GBM) includes a heterogeneous group of tumors. We describe two cases with histopathologically and molecularly similar tumors, but very different outcomes. We attempt to illustrate the need for improved prognostic markers for GBM. CASE DESCRIPTION: Two patients with similar molecular profiles were retrospectively identified. The following markers were assessed: O (6)-methylguanine DNA methyltransferase (MGMT) methylation, isocitrate dehydrogenase (IDH) 1 and 2 status, epidermal growth factor receptor (EGFR) amplification, phosphatase and tensin homolog (PTEN) status, Ki-67, p53, and 1p/19q status. Each patient was assigned a Karnofsky performance score at presentation. Case 1 (62-year-old male) was a right temporal lobe glioblastoma with a molecular profile of amplified EGFR, normal PTEN, no IDH1/2 mutation, 28.7% MGMT promoter methylation, 5-20% Ki-67, 1p deletion, and 19q intact. The patient underwent resection followed by radiation therapy and 2 years of chemotherapy, and was asymptomatic and tumor free 5 years post diagnosis. Tumor eventually recurred and the patient expired 72 months after initial diagnosis. Case 2 (63-year-old male) was a right frontal white matter mass consistent with glioblastoma with a molecular profile of amplified EGFR, absent PTEN, no IDH1/2 mutation, 9.9% MGMT promoter methylation, 5-10%

Ki-67, and 1p/19q status inconclusive. A radical subtotal resection was performed; however, 2 weeks later symptoms had returned. Subsequent imaging revealed a tumor larger than at diagnosis. The patient expired 3 months after initial diagnosis. CONCLUSION: The need for formulating more robust means to classify GBM tumor subtypes is paramount. Standard histopathologic and molecular analyses are costly and did not provide either of these patients with a realistic appraisal of their prognosis. Individualized whole genome testing similar to that being reported for medulloblastoma and other tumors may be preferable to the array of tests as currently utilized.

Menting, J. G., Yang, Y., Chan, S. J., Phillips, N. B., Smith, B. J., Whittaker, J., et al. (2014). Protective hinge in insulin opens to enable its receptor engagement. *Proceedings of the National Academy of Sciences of the United States of America, 111*(33), E3395-404.

Insulin provides a classical model of a globular protein, yet how the hormone changes conformation to engage its receptor has long been enigmatic. Interest has focused on the C-terminal B-chain segment, critical for protective self-assembly in beta cells and receptor binding at target tissues. Insight may be obtained from truncated "microreceptors" that reconstitute the primary hormone-binding site (alpha-subunit domains L1 and alphaCT). We demonstrate that, on microreceptor binding, this segment undergoes concerted hinge-like rotation at its B20-B23 beta-turn, coupling reorientation of Phe(B24) to a 60 degrees rotation of the B25-B28 beta-strand away from the hormone core to lie antiparallel to the receptor's L1-beta2 sheet. Opening of this hinge enables conserved nonpolar side chains (Ile(A2), Val(A3), Val(B12), Phe(B24), and Phe(B25)) to engage the receptor. Restraining the hinge by nonstandard mutagenesis preserves native folding but blocks receptor binding, whereas its engineered opening maintains activity at the price of protein instability and nonnative aggregation. Our findings rationalize properties of clinical mutations in the insulin family and provide a previously unidentified foundation for designing therapeutic analogs. We envisage that a switch between free and receptor-bound conformations of insulin evolved as a solution to conflicting structural determinants of biosynthesis and function.

Michael, T. T., Mogabgab, O., Alomar, M., Kotsia, A., Christopoulos, G., Rangan, B. V., et al. (2014). Long-term outcomes of successful chronic total occlusion percutaneous coronary interventions using the antegrade and retrograde approach. *Journal of Interventional Cardiology,*
OBJECTIVE: To compare long-term clinical outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI) using the retrograde and antegrade approach. BACKGROUND: There is limited long-term clinical outcomes data on the retrograde approach to CTO PCI. METHODS: We performed a retrospective analysis of the long-term clinical outcomes of 193 consecutive patients who underwent successful CTO PCI at our institution between March 2008 and December 2011. RESULTS: Mean age was 63.6 +/- 8.3 years. The target vessel was right coronary artery in 52.6%, left anterior descending artery in 24.5% and circumflex in 21.4% of cases. The retrograde approach was used in 41 patients (21.2%). The mean stent length was longer in the retrograde group (83 +/- 32 vs. 64 +/- 32 mm, P = 0.001). Two major procedural complications occurred, both in the retrograde group (P = 0.012). During a median follow-up of 2.0 years compared to the antegrade CTO PCI group, patients who underwent retrograde CTO PCI were more likely to undergo target lesion revascularization (TLR) (45.6% vs. 25.7%, P = 0.006). No significant difference was observed in the incidence of all-cause mortality, myocardial infarction, non-target vessel revascularization, or coronary artery bypass graft surgery between the 2 groups. On multivariate analysis, stent length was the only independent predictor of TLR during follow-up. CONCLUSIONS: Retrograde CTO PCI was associated with higher incidence of TLR, but similar incidence of death and myocardial infarction compared to antegrade CTO PCI. These findings likely reflect the higher complexity of CTO lesions treated with the retrograde approach.

Midgett, M., Goenezen, S., & Rugonyi, S. (2014). Blood flow dynamics reflect degree of outflow tract banding in hamburger-hamilton stage 18 chicken embryos. *Journal of the Royal Society, Interface / the Royal Society, 11*(100), 10.1098/rsif.2014.0643.
Altered blood flow during embryonic development has been shown to cause cardiac defects; however, the mechanisms by which the resulting haemodynamic forces trigger heart malformation are unclear. This study used heart outflow tract banding to alter normal haemodynamics in a chick embryo model at HH18 and characterized the immediate blood flow

response versus the degree of band tightness. Optical coherence tomography was used to acquire two-dimensional longitudinal structure and Doppler velocity images from control (n = 16) and banded (n = 25, 6-64% measured band tightness) embryos, from which structural and velocity data were extracted to estimate haemodynamic measures. Peak blood flow velocity and wall shear rate (WSR) initially increased linearly with band tightness (p 0.1). The haemodynamic dependence on the degree of banding reveals immediate adaptations of the early embryonic cardiovascular system and could help elucidate a range of cardiac adaptations to gradually increased load.

Minei, J. P., Fabian, T. C., Guffey, D. M., Newgard, C. D., Bulger, E. M., Brasel, K. J., et al. (2014). Increased trauma center volume is associated with improved survival after severe injury: Results of a resuscitation outcomes consortium study. *Annals of Surgery, 260*(3), 456-465. OBJECTIVE: To investigate the relationship between trauma center volume and outcome. BACKGROUND: The Resuscitation Outcomes Consortium is a network of 11 centers and 60 hospitals conducting emergency care research. For many procedures, high-volume centers demonstrate superior outcomes versus low-volume centers. This remains controversial for trauma center outcomes. METHODS: This study was a secondary analysis of prospectively collected data from the Resuscitation Outcomes Consortium multicenter out-of-hospital Hypertonic Saline Trial in patients with Glasgow Coma Scale score of 8 or less (traumatic brain injury) or systolic blood pressure of 90 or less and pulse of 110 or more (shock). Regression analyses evaluated associations between trauma volume and the following outcomes: 24-hour mortality, 28-day mortality, ventilator-free days, Multiple Organ Dysfunction Scale incidence, worst Multiple Organ Dysfunction Scale score, and poor 6-month Glasgow Outcome Scale-Extended score. RESULTS: A total of 2070 patients were evaluated: 1251 in the traumatic brain injury cohort and 819 in the shock cohort. Overall, 24-hour and 28-day mortality was 16% and 25%, respectively. For every increase of 500 trauma center admissions, there was a 7% decreased odds of 24-hour and 28-day mortality for all patients. As trauma center volume increased, nonorgan dysfunction complications increased, ventilator-free days increased, and worst Multiple Organ Dysfunction Scale score decreased. The associations with higher trauma center volume were similar for the traumatic brain injury cohort, including better neurologic

outcomes at 6 months, but not for the shock cohort. CONCLUSIONS: Increased trauma center volume was associated with increased survival, more ventilator-free days, and less severe organ failure. Trauma system planning and implementation should avoid unnecessary duplication of services.

Mitin, T., & Zietman, A. L. (2014). Promise and pitfalls of heavy-particle therapy. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,*

Proton beam therapy, the most common form of heavy-particle radiation therapy, is not a new invention, but it has gained considerable public attention because of the high cost of installing and operating the rapidly increasing number of treatment centers. This article reviews the physical properties of proton beam therapy and focuses on the up-to-date clinical evidence comparing proton beam therapy with the more standard and widely available radiation therapy treatment alternatives. In a cost-conscious era of health care, the hypothetical benefits of proton beam therapy will have to be supported by demonstrable clinical gains. Proton beam therapy represents, through its scale and its cost, a battleground for the policy debate around managing expensive technology in modern medicine.

Mok, G. T. K., Chiang, J. P. W., Yeung, J. C. C., & Chung, B. H. Y. (2014). Clinical quiz (p207) answer. *Hong Kong Journal of Paediatrics, 19*(3), 216-219.

Mok, G. T. K., Chiang, J. P. W., Yeung, J. C. C., & Chung, B. H. Y. (2014). What is the diagnosis? *Hong Kong Journal of Paediatrics, 19*(3), 207.

Moldt, B., Saye-Francisco, K., Schultz, N., Burton, D. R., & Hessell, A. J. (2014). Simplifying the synthesis of SIgA: Combination of dIgA and rhSC using affinity chromatography. *Methods (San Diego, Calif.), 65*(1), 127-132.

The mucosal epithelia together with adaptive immune responses, such as local production and secretion of dimeric and polymeric immunoglobulin A (IgA), are a crucial part of the first line of defense against invading pathogens. IgA is primarily secreted as SIgA and plays multiple roles in mucosal defense. The study of SIgA-mediated protection is an important area of research in mucosal immunity but an easy, fast and reproducible method to generate pathogen-specific SIgA

in vitro has not been available. We report here a new method to produce SIgA by co-purification of dimeric IgA, containing J chain, and recombinant human SC expressed in CHO cells. We previously reported the generation, production and characterization of the human recombinant monoclonal antibody IgA2 b12. This antibody, derived from the variable regions of the neutralizing anti-HIV-1 mAb IgG1 b12, blocked viral attachment and uptake by epithelial cells in vitro. We used a cloned CHO cell line that expresses monomeric, dimeric and polymeric species of IgA2 b12 for large-scale production of dIgA2 b12. Subsequently, we generated a CHO cell line to express recombinant human secretory component (rhSC). Here, we combined dIgA2 b12 and CHO-expressed rhSC via column chromatography to produce SIgA2 b12 that remains fully intact upon elution with 0.1M citric acid, pH 3.0. We have performed biochemical analysis of the synthesized SIgA to confirm the species is of the expected size and retains the functional properties previously described for IgA2 b12. We show that SIgA2 b12 binds to the HIV-1 gp120 glycoprotein with similar apparent affinity to that of monomeric and dimeric forms of IgA2 b12 and neutralizes HIV-1 isolates with similar potency. An average yield of 6 mg of SIgA2 b12 was achieved from the combination of 20mg of purified dIgA2 b12 and 2L of rhSC-containing CHO cell supernatant. We conclude that synthesized production of stable SIgA can be generated by co-purification. This process introduces a simplified means of generating a variety of pathogen-specific SIgA antibodies for research and clinical applications.

Mooney, M. A., Nigg, J. T., McWeeney, S. K., & Wilmot, B. (2014). Functional and genomic context in pathway analysis of GWAS data. *Trends in Genetics : TIG, 30*(9), 390-400.

Gene set analysis (GSA) is a promising tool for uncovering the polygenic effects associated with complex diseases. However, the available techniques reflect a wide variety of hypotheses about how genetic effects interact to contribute to disease susceptibility. The lack of consensus about the best way to perform GSA has led to confusion in the field and has made it difficult to compare results across methods. A clear understanding of the various choices made during GSA - such as how gene sets are defined, how single-nucleotide polymorphisms (SNPs) are assigned to genes, and how individual SNP-level effects are aggregated to produce gene- or pathway-level effects - will improve the interpretability and comparability of results across methods and studies. In this review we provide an overview of the various data sources used to construct gene sets and the

statistical methods used to test for gene set association, as well as provide guidelines for ensuring the comparability of results.

Myers, P. J., Griest, S., Kaelin, C., Legro, M. W., Schmidt, C. J., Zaugg, T. L., et al. (2014). Development of a progressive audiologic tinnitus management program for veterans with tinnitus. *Journal of Rehabilitation Research and Development, 51*(4), 609-622.
Tinnitus is the most prevalent service-connected disability awarded to Veterans. However, clinical protocols for management of tinnitus have been inconsistent across Department of Veterans Affairs (VA) medical centers. A study was funded to develop and pilot test a protocol to provide tinnitus services consistently across VA audiology clinics. Drawing on a series of prior VA and external research projects, a clinical model was formulated, supporting materials in multimedia were developed, and a pilot study was conducted. Five hierarchical levels of care were defined and labeled the Progressive Audiologic Tinnitus Management (PATM) model. The model facilitates access to medical services for tinnitus and includes detailed protocols for evaluation, education, and counseling of patients. Patients at each level of care have the option to "progress" to the next level of PATM if further services are required. Clinical procedures were defined for each level and materials were produced for audiologists and patients. The PATM model was then piloted with clinical patients at the James A. Haley Veterans' Hospital (JAHVH) in Tampa, Florida. Throughout the pilot study, feedback from patients and clinicians was carefully noted. Training materials for audiologists, incorporation of the protocol into clinic activities, and patient outcomes were evaluated. The model was implemented within the JAHVH Audiology Clinic and to assist Veterans with tinnitus management. The most notable finding was how little tinnitus-specific intervention was required for the majority of patients. This finding supports a clinical model that offers stepped-care ("progressive") levels of care until tinnitus management is achieved by the patient.

Nagel, B. J., Herting, M. M., & Cservenka, A. (2013). *Working memory and addictive behavior* Taylor and Francis.

Nappi, R. E., Serrani, M., & Jensen, J. T. (2014). Noncontraceptive benefits of the estradiol valerate/dienogest combined oral contraceptive: A review of the literature. *International Journal of Women's Health, 6*, 711-718.

Combined oral contraceptives formulated to include estradiol (E2) have recently become available for the indication of pregnancy prevention. A combined estradiol valerate and dienogest pill (E2V/DNG), designed to be administered using an estrogen step-down and a progestin step-up regimen over 26 days of active treatment followed by 2 days of placebo (26/2-day regimen), has also undergone research to assess the potential for additional noncontraceptive benefits. Randomized, placebo-controlled studies have demonstrated that E2V/DNG is an effective treatment for heavy menstrual bleeding - a reduction in median menstrual blood loss approaching 90% occurs after 6 months of treatment. To date, E2V/DNG is the only oral contraceptive approved for this indication. Comparator studies have also demonstrated a reduction in hormone withdrawal-associated symptoms in users of E2V/DNG compared with a conventional 21/7-day regimen of ethinylestradiol/levonorgestrel. Other potential noncontraceptive benefits associated with E2V/DNG, like improvement in dysmenorrhea, sexual function, and quality of life, are comparable with those associated with other combined oral contraceptives and are discussed further in this review.

Nguyen, B. T., & Jensen, J. T. (2014). Evaluating the efficacy and safety of a progestin- and estrogen-releasing ethylene vinyl acetate copolymer contraceptive vaginal ring. *Expert Opinion on Drug Safety,* , 1-8.

Introduction: Multiple studies confirm the safety and efficacy of the combined ethinyl estradiol (EE) and etonogestrel contraceptive vaginal ring (NuvaRing(R)). Advantages of continuous drug delivery through the vagina compared to oral administration include stable levels of contraceptive steroids without the need for daily drug administration. Although the combined contraceptive vaginal ring (CCVR) avoids the problem of missed pills, clinical data do not support greater efficacy. Vaginal administration avoids first-pass hepatic effects; however, EE is a potent inducer of hepatic globulins regardless of the route of administration. Consequently, thromboembolic risk during CCVR use is similar to that with combined oral contraceptives. Some epidemiologic and database studies suggest that the risk of thromboembolism is increased among users of the CCVR compared to levonorgestrel-containing combined pills. Areas covered: This review examined the available literature for level 1 and level 2 evidence of the CCVR and its associated efficacy and safety. Studies are presented in table format with significant findings and

conclusions described. Expert opinion: A prospective study with 33,235 woman-years of exposure and with greater ability to control for covariates did not demonstrate an elevation of risk. The safety profile of the CCVR appears to be the same as with other combined hormonal contraceptives.

Nicolaidis, C., Kripke, C. C., & Raymaker, D. (2014). Primary care for adults on the autism spectrum. *The Medical Clinics of North America, 98*(5), 1169-1191.

Autism spectrum disorder (ASD) is defined by differences in social communication and restricted, repetitive patterns of behavior, interests, or activities. Skills and challenges can change depending on environmental stimuli, supports, and stressors. Quality of life can be improved by the use of accommodations, assistive technologies, therapies to improve adaptive function or communication, caregiver training, acceptance, access, and inclusion. This article focuses on the identification of ASD in adults, referrals for services, the recognition of associated conditions, strategies and accommodations to facilitate effective primary care services, and ethical issues related to caring for autistic adults.

Nigg, J. T., & Holton, K. (2014). Restriction and elimination diets in ADHD treatment. *Child and Adolescent Psychiatric Clinics of North America,*

Food elimination diets are defined and the history of their investigation in relation to attention-deficit/hyperactivity disorder (ADHD) is reviewed. After noting that a consensus has emerged that an elimination diet produces a small but reliable aggregate effect, the present review provides updated quantitative estimates of effect size and clinical response rates to elimination diets. It then highlights key issues that require research attention, in particular characterization of dietary responders. Finally, because some children may benefit, clinical guidelines at the present state of knowledge are summarized. It is concluded that updated trials of elimination diets are sorely needed for ADHD. © 2014 Elsevier Inc. All rights reserved.

Nzabarushimana, E., Miousse, I. R., Shao, L., Chang, J., Allen, A. R., Turner, J., et al. (2014). Long-term epigenetic effects of exposure to low doses of 56Fe in the mouse lung. *Journal of Radiation Research, 55*(4), 823-828.

Despite significant progress, the long-term health effects of exposure to high charge (Z) and

energy (E) nuclei (HZEs) and the underlying mechanisms remain poorly understood. Mouse studies show that space missions can result in pulmonary pathological states. The goal of this study was to evaluate the pro-fibrotic and pro-carcinogenic effects of exposure to low doses of heavy iron ions (56Fe) in the mouse lung. Exposure to 56Fe (600 MeV; 0.1, 0.2 and 0.4 Gy) resulted in minor pro-fibrotic changes, detected at the beginning of the fibrotic phase (22 weeks post exposure), which were exhibited as increased expression of chemokine Ccl3, and interleukin Il4. Epigenetic alterations were exhibited as global DNA hypermethylation, observed after exposure to 0.4 Gy. Cadm1, Cdh13, Cdkn1c, Mthfr and Sfrp1 were significantly hypermethylated after exposure to 0.1 Gy, while exposure to higher doses resulted in hypermethylation of Cdkn1c only. However, expression of these genes was not affected by any dose. Congruently with the observed patterns of global DNA methylation, DNA repetitive elements were hypermethylated after exposure to 0.4 Gy, with minor changes observed after exposure to lower doses. Importantly, hypermethylation of repetitive elements coincided with their transcriptional repression. The findings of this study will aid in understanding molecular determinants of pathological states associated with exposure to 56Fe, as well as serve as robust biomarkers for the delayed effects of irradiation. Further studies are clearly needed to investigate the persistence and outcomes of molecular alterations long term after exposure. © 2014 The Author.

Oates, C. J., Dondelinger, F., Bayani, N., Korkola, J., Gray, J. W., & Mukherjee, S. (2014). Causal network inference using biochemical kinetics. *Bioinformatics (Oxford, England), 30*(17), i468-i474.

MOTIVATION: Networks are widely used as structural summaries of biochemical systems. Statistical estimation of networks is usually based on linear or discrete models. However, the dynamics of biochemical systems are generally non-linear, suggesting that suitable non-linear formulations may offer gains with respect to causal network inference and aid in associated prediction problems. RESULTS: We present a general framework for network inference and dynamical prediction using time course data that is rooted in non-linear biochemical kinetics. This is achieved by considering a dynamical system based on a chemical reaction graph with associated kinetic parameters. Both the graph and kinetic parameters are treated as unknown; inference is carried out within a Bayesian framework. This allows prediction of dynamical behavior

even when the underlying reaction graph itself is unknown or uncertain. Results, based on (i) data simulated from a mechanistic model of mitogen-activated protein kinase signaling and (ii) phosphoproteomic data from cancer cell lines, demonstrate that non-linear formulations can yield gains in causal network inference and permit dynamical prediction and uncertainty quantification in the challenging setting where the reaction graph is unknown. AVAILABILITY AND IMPLEMENTATION: MATLAB R2014a software is available to download from warwick.ac.uk/chrisoates. CONTACT: c.oates@warwick.ac.uk or sach@mrc-bsu.cam.ac.uk SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.

Oehler, A., & Shah, S. (2014). Myopericarditis in a pregnant woman with acute promyelocytic leukemia. *Journal of Cardiology Cases,*

Acute promyelocytic leukemia (APL) is a form of acute leukemia with a characteristic translocation, t(15;17), and is considered a hematologic emergency, typically treated with all-trans retinoic acid and an anthracycline. We present the case of a young, gravid woman who was diagnosed with APL in the third trimester, initiated typical treatment, and suffered uncommon cardiac complications. . © 2014 Japanese College of Cardiology.

Oellrich, A., Koehler, S., Washington, N., Sanger Mouse Genetic Project, Mungall, C., Lewis, S., et al. (2014). The influence of disease categories on gene candidate predictions from model organism phenotypes. *Journal of Biomedical Semantics, 5*(Suppl 1 Proceedings of the Bio-Ontologies Spec Interest G), S4-1480-5-S1-S4. eCollection 2014.

BACKGROUND: The molecular etiology is still to be identified for about half of the currently described Mendelian diseases in humans, thereby hindering efforts to find treatments or preventive measures. Advances, such as new sequencing technologies, have led to increasing amounts of data becoming available with which to address the problem of identifying disease genes. Therefore, automated methods are needed that reliably predict disease gene candidates based on available data. We have recently developed Exomiser as a tool for identifying causative variants from exome analysis results by filtering and prioritising using a number of criteria including the phenotype similarity between the disease and mouse mutants involving the gene candidates. Initial investigations revealed a variation in performance for different medical

categories of disease, due in part to a varying contribution of the phenotype scoring component. RESULTS: In this study, we further analyse the performance of our cross-species phenotype matching algorithm, and examine in more detail the reasons why disease gene filtering based on phenotype data works better for certain disease categories than others. We found that in addition to misleading phenotype alignments between species, some disease categories are still more amenable to automated predictions than others, and that this often ties in with community perceptions on how well the organism works as model. CONCLUSIONS: In conclusion, our automated disease gene candidate predictions are highly dependent on the organism used for the predictions and the disease category being studied. Future work on computational disease gene prediction using phenotype data would benefit from methods that take into account the disease category and the source of model organism data.

Offner, H. (2014). Modeling immunity and inflammation in stroke: Don't be afraid of mice? *Stroke; a Journal of Cerebral Circulation, 45*(9), e181-2.

Orfila, J. E., Shimizu, K., Garske, A. K., Deng, G., Maylie, J., Traystman, R. J., et al. (2014). Increasing small conductance Ca2+-activated potassium channel activity reverses ischemia-induced impairment of long-term potentiation. *European Journal of Neuroscience,*
Global cerebral ischemia following cardiac arrest and cardiopulmonary resuscitation (CA/CPR) causes injury to hippocampal CA1 pyramidal neurons and impairs cognition. Small conductance Ca2+-activated potassium channels type 2 (SK2), expressed in CA1 pyramidal neurons, have been implicated as potential protective targets. Here we showed that, in mice, hippocampal long-term potentiation (LTP) was impaired as early as 3 h after recovery from CA/CPR and LTP remained impaired for at least 30 days. Treatment with the SK2 channel agonist 1-Ethyl-2-benzimidazolinone (1-EBIO) at 30 min after CA provided sustained protection from plasticity deficits, with LTP being maintained at control levels at 30 days after recovery from CA/CPR. Minimal changes in glutamate release probability were observed at delayed times after CA/CPR, implicating post-synaptic mechanisms. Real-time quantitative reverse transcriptase-polymerase chain reaction indicated that CA/CPR did not cause a loss of N-methyl-D-aspartate (NMDA) receptor mRNA at 7 or 30 days after CA/CPR. Similarly, no change in synaptic NMDA receptor

protein levels was observed at 7 or 30 days after CA/CPR. Further, patch-clamp experiments demonstrated no change in functional synaptic NMDA receptors at 7 or 30 days after CA/CPR. Electrophysiology recordings showed that synaptic SK channel activity was reduced for the duration of experiments performed (up to 30 days) and that, surprisingly, treatment with 1-EBIO did not prevent the CA/CPR-induced loss of synaptic SK channel function. We concluded that CA/CPR caused alterations in post-synaptic signaling that were prevented by treatment with the SK2 agonist 1-EBIO, indicating that activators of SK2 channels may be useful therapeutic agents to prevent ischemic injury and cognitive impairments.

Ostrowski, K. A., Polackwich, A. S., Kent, J., Conlin, M. J., Hedges, J. C., & Fuchs, E. F. (2014). Higher outcomes of vasectomy reversal for men with the same female partner as before the vasectomy. *The Journal of Urology,*

PURPOSE: To review fertility outcomes of vasectomy reversals in men with the same female partners as before their vasectomy from a high surgical volume center. MATERIALS & METHODS: A retrospective study of a prospective database was performed. All vasectomy reversals were performed by a single surgeon (EFF). Patients undergoing microsurgical vasectomy reversal with the same female partners as before the vasectomy were identified from 1978 to 2011. Pregnancy rates, live birth rates, type of procedure (bilateral vasovasostomy, bilateral vasoepididymostomy, unilateral vasovasostomy, or unilateral vasoepididymostomy), patency rates, time from reversal, and age of spouse were evaluated. RESULTS: A total of 3,135 consecutive microsurgical vasectomy reversals were reviewed. Of these patients, 524 (17%) underwent vasectomy reversal with the same female partner. A total of 258 patients (49%) had complete information available, and had a vas patency rate of 94%. Clinical pregnancy rate was 83% with natural means (compared to 60% in our general vasectomy reversal population ($p<0.0001$)). Logistic regression analysis controlling for wife age, patient age, and years from vasectomy and vasectomy reversal with the same female partner had an odds ratio of 2 ($p<0.007$). The average time interval from vasectomy was 5.7 years. The average age of the patient at reversal was 38.9 years and average age of the female partner was 33.2 years. CONCLUSIONS: Outcomes of clinical pregnancy and live birth rates are higher in men undergoing microsurgical vasectomy reversal with the same

female partner. These outcomes may be related to shorter interval from vasectomy, previous fertility, and motivation of the couple.

Pagel, J. M., Spurgeon, S. E., Byrd, J. C., Awan, F. T., Flinn, I. W., Lanasa, M. C., et al. (2014). Otlertuzumab (TRU-016), an anti-CD37 monospecific ADAPTIR™ therapeutic protein, for relapsed or refractory NHL patients. *British Journal of Haematology,*

CD37 is cell surface tetraspanin present on normal and malignant B cells. Otlertuzumab (TRU-016) is a novel humanized anti-CD37 protein therapeutic. Patients with relapsed or refractory follicular non-Hodgkin lymphoma (FL), mantle cell lymphoma (MCL), or Waldenström's macroglobulinaemia (WM) received otlertuzumab at 20 mg/kg administered intravenously once a week for up to 8 weeks followed by 4 monthly doses. Sixteen patients were treated; median age was 62·5 years (range, 41-81), and median number of prior regimens was 4 (range, 1-7). Twelve patients were refractory to prior treatment, 5 were refractory to rituximab. The mean terminal half-life was 9·5 days. Lymph node reduction of =50% by computerized tomography scan measurements was seen in 3 of 12 patients, including one FL patient who had a partial response. One WM patient had a minor response. The most frequent adverse events were neutropenia, fatigue, nausea, thrombocytopenia, diarrhoea, and peripheral oedema; most were grade 1/2. Otlertuzumab treatment appears to have been well tolerated by the patients in this study. Clinical activity was observed in this small heterogeneous cohort of highly refractory, heavily pretreated B-cell non-Hodgkin lymphoma patients. These data suggest that further clinical investigation in non-Hodgkin lymphoma is warranted.

Park, J. Y., Mott, M., Williams, T., Ikeda, H., Wen, H., Linhoff, M., et al. (2014). A single mutation in the acetylcholine receptor delta-subunit causes distinct effects in two types of neuromuscular synapses. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 34*(31), 10211-10218.

Mutations in AChR subunits, expressed as pentamers in neuromuscular junctions (NMJs), cause various types of congenital myasthenic syndromes. In AChR pentamers, the adult epsilon subunit gradually replaces the embryonic gamma subunit as the animal develops. Because of this switch in subunit composition, mutations in specific subunits result in synaptic phenotypes that change

with developmental age. However, a mutation in any AChR subunit is considered to affect the NMJs of all muscle fibers equally. Here, we report a zebrafish mutant of the AChR delta subunit that exhibits two distinct NMJ phenotypes specific to two muscle fiber types: slow or fast. Homozygous fish harboring a point mutation in the delta subunit form functional AChRs in slow muscles, whereas receptors in fast muscles are nonfunctional. To test the hypothesis that different subunit compositions in slow and fast muscles underlie distinct phenotypes, we examined the presence of epsilon/gamma subunits in NMJs using specific antibodies. Both wild-type and mutant larvae lacked epsilon/gamma subunits in slow muscle synapses. These findings in zebrafish suggest that some mutations in human congenital myasthenic syndromes may affect slow and fast muscle fibers differently.

Peterson, H., Lofgren, S., Bremmer, S., & Krol, A. (2013). Novel ABCA-12 mutations leading to recessive congenital ichthyosis. *Pediatric Dermatology, 30*(6), e236-7.

Mutations in the keratinocyte lipid transporter adenosine triphosphate-binding cassette A12 (ABCA12) are known to cause harlequin ichthyosis. More recently, mutations in this gene have been demonstrated to cause other phenotypes within the spectrum of recessive congenital ichthyosis. We report the case of an infant with novel heterozygous mutations in ABCA12 who exhibited features and a clinical course more consistent with congenital ichthyosiform erythroderma than harlequin ichthyosis.

Phan, I. T., Courtney, R. J., Marx, D. P., Wilson, D. J., Mansoor, A., & Ng, J. D. (2014). Proptosis caused by rhabdomyomatous mesenchymal hamartomata occurring in the orbit. *Ophthalmic Plastic and Reconstructive Surgery,*

Two infants were referred for progressive orbital proptosis. MRI in both cases demonstrated a homogenous mass in the orbit adherent to and isointense with a rectus muscle. Histopathology in both cases demonstrated a bland proliferation of spindle cells with entrapped skeletal muscle. Immunochemistry demonstrated that the abnormal tissue was of skeletal muscle origin, consistent with rhabdomyomatous mesenchymal hamartoma (RMH). Observation was elected due to the reported benign nature of RMH. In contrast to RMH of the cutaneous tissues that typically follows a benign course, RMH of the orbit may present with rapid growth.

Port, A. D., Chan, R. V. P., Ostmo, S., Choi, D., & Chiang, M. F. (2014). Risk factors for retinopathy of prematurity: Insights from outlier infants. *Graefe's Archive for Clinical and Experimental Ophthalmology,*

Purpose To investigate the characteristics of outlier infants for insights into ROP risk. Methods Chart data were collected from 1,354 infants screened for ROP at Weill Cornell Medical Center and Columbia University Medical Center. ROP exam results and clinical risk factors were recorded. The cohort was stratified by weight, highest ROP stage, and need for ROP treatment. Descriptive and correlational statistics were performed. Results For the overall cohort, regression analysis found that birth weight (OR: 0.741 per 100 g; 95 % CI: 0.606, 0.905), gestational age at birth (OR: 0.563 per week; 95 % CI: 0.454, 0.697), multiple gestation (OR 2.02, 95 % CI: 1.15, 3.56), bronchopulmonary dysplasia (OR: 4.68, 95 % CI: 1.93, 11.35), and necrotizing enterocolitis (OR 2.80, 95 % CI: 1.40, 5.16) were independent risk factors for treatment-requiring ROP. Black race was found to be a protective factor for treatment-requiring ROP (OR 0.244, 95 % CI: 0.095, 0.626). Among 15 infants with BW 1500 g, the 17 (9 %) with ROP only differed from the 166 (91 %) without ROP with respect to a higher incidence of necrotizing enterocolitis among those with ROP (11.8 % vs 0 %). Conclusions Although known clinical risk factors were predictive of ROP stage and need for laser treatment in this cohort, they were not significantly associated with ROP at extremes of birth weight. This suggests that other clinical, maternal, or genetic factors may protect from or predispose to ROP. © 2014 Springer-Verlag Berlin Heidelberg.

Porter, T. R., Abdelmoneim, S., Belcik, J. T., McCulloch, M. L., Mulvagh, S. L., Olson, J. J., et al. (2014). Guidelines for the cardiac sonographer in the performance of contrast echocardiography: A focused update from the american society of echocardiography. *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography, 27*(8), 797-810.

Puchner, S. B., Liu, T., Mayrhofer, T., Truong, Q. A., Lee, H., Fleg, J. L., et al. (2014). High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: Results from the ROMICAT-II trial. *Journal of the*

American College of Cardiology, 64(7), 684-692.

BACKGROUND: It is not known whether high-risk plaque, as detected by coronary computed tomography angiography (CTA), permits improved early diagnosis of acute coronary syndromes (ACS) independently to the presence of significant coronary artery disease (CAD) in patients with acute chest pain. OBJECTIVES: The primary aim of this study was to determine whether high-risk plaque features, as detected by CTA in the emergency department (ED), may improve diagnostic certainty of ACS independently and incrementally to the presence of significant CAD and clinical risk assessment in patients with acute chest pain but without objective evidence of myocardial ischemia or myocardial infarction (MI). METHODS: We included patients randomized to the coronary CTA arm of the ROMICAT-II (Rule Out Myocardial Infarction/Ischemia Using Computer-Assisted Tomography II) trial. Readers assessed coronary CTA qualitatively for the presence of nonobstructive CAD (1% to 49% stenosis), significant CAD (>/=50% or >/=70% stenosis), and the presence of at least 1 of the high-risk plaque features (positive remodeling, low /=50% stenosis in 45 patients [9.5%]). High-risk plaques were more frequent in patients with ACS and remained a significant predictor of ACS (odds ratio [OR]: 8.9; 95% CI: 1.8 to 43.3; p = 0.006) after adjustment for >/=50% stenosis (OR: 38.6; 95% CI: 14.2 to 104.7; p /=70% stenosis. CONCLUSIONS: In patients presenting to the ED with acute chest pain but negative initial electrocardiogram and troponin, presence of high-risk plaques on coronary CTA increased the likelihood of ACS independent of significant CAD and clinical risk assessment (age, sex, and number of cardiovascular risk factors). (Multicenter Study to Rule Out Myocardial Infarction by Cardiac Computed Tomography [ROMICAT-II]; NCT01084239).

Ragel, B. T., Mendez, G. A., Reddington, J., Ferachi, D., Kubicky, C. D., Philipp, T. C., et al. (2014). Life expectancy and metastatic spine scoring systems: An academic institutional experience. *Journal of Spinal Disorders & Techniques,*

STUDY DESIGN:: A retrospective data collection study with application of metastatic spine scoring systems. OBJECTIVES:: To apply the Tomita and revised Tokuhashi scoring systems to a surgical cohort at a single academic institution and analyze spine-related surgical morbidity and mortality rates. SUMMARYOF BACKGROUND DATA:: Surgical management of metastatic spine patients requires tools that can accurately predict patient survival, as well as knowledge of

morbidity and mortality rates. METHODS:: An Oregon Health & Science University (OHSU) Spine Center surgical database was queried (years 2002 to 2010) to identify patients with an ICD-9 code indicative of metastatic spine disease. Patients whose only surgical treatment was vertebral augmentation were not included. Scatter plots of survival versus the Tomita and revised Tokuashi metastatic spine scoring systems were statistically analyzed. Spine-related morbidity and mortality rates were calculated. RESULTS:: Sixty-eight patients were identified; 45 patients' (30 male, mean age 45 y) medical records included operative, morbidity and mortality statistic data and 38 (26 male, mean age 54 y) contained complete metastatic spine scoring system data. Of the 38 deceased spine metastatic patients; 8 had renal cell, 7 lung, 4 breast, 2 chondrosarcoma, 2 prostate, 11 other, and 4 unknown primary cancers. Linear regression analysis revealed R values of 0.2570 and 0.2009 for the revised Tokohashi and Tomita scoring systems, respectively. Overall transfusion, infection, morbidity, and mortality rates were 33% and 9%, and 42% and 9%, respectively. CONCLUSIONS:: Application of metastatic prognostic scoring systems to a retrospective surgical cohort revealed an overall poor correlation with the Tomita and revised Tokuhashi predictive survival models. Morbidity and mortality rates concur with those in the medical literature. This study underscores the difficulty in utilizing metastatic spine scoring systems to predict patient survival. We believe a scoring system based on cancer type is needed to account for changes in treatment paradigms with improved patient survival over time.

Rajpurkar, M., Chitlur, M., Recht, M., & Cooper, D. L. (2014). Use of recombinant activated factor VII in patients with glanzmann's thrombasthenia: A review of the literature. *Haemophilia, 20*(4), 464-471.

Glanzmann's thrombasthenia (GT) is a rare bleeding disorder characterized by a quantitative or qualitative defect of glycoprotein IIb/IIIa on the platelet membrane. Managing bleeding episodes is often difficult, and a variety of modalities have been used, including platelet transfusions, recombinant factor VIIa (rFVIIa), and other supportive care. The aim of this review was to present the clinical experience with rFVIIa bolus infusion (rFVIIa BI) for treatment of bleeding episodes and prevention of bleeding during surgical procedures in patients with GT. A literature search was performed to identify rFVIIa-treated patients with GT. Overall, one international survey, one open-label study, and 40 case reports identified 172 bleeding episodes treated with

rFVIIa and 62 procedures covered with rFVIIa. In the international survey, rFVIIa BI was used for 96 bleeding episodes in 59 patients. Recombinant FVIIa was effective in 76 bleeding episodes (79%). Of 34 surgical procedures, 25 procedures received rFVIIa BI with 92% bleeding-prevention efficacy. The open-label study reported 28 patients with 28 rFVIIa BI-treated bleeds, and 26 (93%) bleeding episodes responded to rFVIIa. Published case reports revealed that 25 (69%) of 36 bleeds and 27 (96%) of 28 surgeries responded to rFVIIa BI treatment. Overall, 26 adverse events were reported in 19 patients, including five thromboembolic events in two patients where a possible relationship with rFVIIa could not be excluded. Two large studies and 40 case reports provide a literature base to support the efficacy and safety of rFVIIa BI in patients with GT.

Rasanen, J., Quinn, M. J., Laurie, A., Bean, E., Roberts, C. T.,Jr, Nagalla, S. R., et al. (2014). Maternal serum glycosylated fibronectin as a point-of-care biomarker for assessment of preeclampsia. *American Journal of Obstetrics and Gynecology,*

OBJECTIVE: We assessed the association of glycosylated fibronectin (GlyFn) with preeclampsia and its performance in a point-of-care (POC) test. STUDY DESIGN: GlyFn, placental growth factor (PlGF), and soluble vascular endothelial growth factor receptor 1 (sFlt1) levels were determined in serum samples from 107 pregnant women. In all, 45 were normotensive and 62 were diagnosed with preeclampsia. The ability of GlyFn to assess preeclampsia status and relationships between GlyFn and maternal characteristics and pregnancy outcomes were analyzed. RESULTS: GlyFn serum levels in the first trimester were significantly higher in women with preeclampsia ($P < .01$) and remained higher throughout pregnancy ($P < .01$). GlyFn, sFlt1, PlGF, and the sFlt1/PlGF ratio were significantly associated ($P < .01$) with preeclampsia status, and the classification performance of these analytes represented by area under the receiver operating characteristic curve was 0.99, 0.96, 0.94, and 0.98, respectively, with 95% confidence intervals of 0.98-1.00, 0.89-1.00, 0.86-1.00, and 0.94-1.00, respectively. Increased GlyFn levels were significantly associated with gestational age at delivery ($P < .01$), blood pressure ($P = .04$), and small-for-gestational-age neonates. Repeated-measures analysis of the difference in weekly GlyFn change in the third trimester demonstrated that mild preeclampsia was associated with a weekly change of 81.7 mug/mL (SE 94.1) vs 195.2 mug/mL (SE 88.2) for severe preeclampsia.

The GlyFn POC demonstrated similar performance to a plate assay with an area under the receiver operating characteristic curve of 0.93 and 95% confidence interval of 0.85-1.00. CONCLUSION: GlyFn is a robust biomarker for monitoring of preeclampsia in both a standard and POC format, which supports its utility in diverse settings.

Rashid, S., Tavori, H., Brown, P. E., Linton, M. F., He, J., Giunzioni, I., et al. (2014). Proprotein convertase subtilisin kexin type 9 promotes intestinal overproduction of triglyceride-rich apolipoprotein B lipoproteins through both low-density lipoprotein receptor-dependent and -independent mechanisms. *Circulation, 130*(5), 431-441.

BACKGROUND: Proprotein convertase subtilisin kexin type 9 (PCSK9) promotes the degradation of the low-density lipoprotein (LDL) receptor (LDLR), and its deficiency in humans results in low plasma LDL cholesterol and protection against coronary heart disease. Recent evidence indicates that PCSK9 also modulates the metabolism of triglyceride-rich apolipoprotein B (apoB) lipoproteins, another important coronary heart disease risk factor. Here, we studied the effects of physiological levels of PCSK9 on intestinal triglyceride-rich apoB lipoprotein production and elucidated for the first time the cellular and molecular mechanisms involved. METHODS AND RESULTS: Treatment of human enterocytes (CaCo-2 cells) with recombinant human PCSK9 (10 mug/mL for 24 hours) increased cellular and secreted apoB48 and apoB100 by 40% to 55% each ($P<0.01$ versus untreated cells), whereas short-term deletion of PCSK9 expression reversed this effect. PCSK9 stimulation of apoB was due to a 1.5-fold increase in apoB mRNA ($P<0.01$) and to enhanced apoB protein stability through both LDLR-dependent and LDLR-independent mechanisms. PCSK9 decreased LDLR protein ($P<0.01$) and increased cellular apoB stability via activation of microsomal triglyceride transfer protein. PCSK9 also increased levels of the lipid-generating enzymes FAS, SCD, and DGAT2 ($P<0.05$). In mice, human PCSK9 at physiological levels increased intestinal microsomal triglyceride transfer protein levels and activity regardless of LDLR expression. CONCLUSIONS: PCSK9 markedly increases intestinal triglyceride-rich apoB production through mechanisms mediated in part by transcriptional effects on apoB, microsomal triglyceride transfer protein, and lipogenic genes and in part by posttranscriptional effects on the LDLR and microsomal triglyceride transfer protein. These findings indicate that targeted PCSK9-based therapies may also be effective in the management of postprandial hypertriglyceridemia.

Raslan, A. M., & Burchiel, K. J. (2014). Value-based neurosurgery and microvascular decompression. *Journal of Neurosurgery, 121*(2), 495-496.

Ray, S., Miller, M., Karalunas, S., Robertson, C., Grayson, D. S., Cary, R. P., et al. (2014). Structural and functional connectivity of the human brain in autism spectrum disorders and attention-deficit/hyperactivity disorder: A rich club-organization study. *Human Brain Mapping,* Attention-deficit/hyperactive disorder (ADHD) and autism spectrum disorders (ASD) are two of the most common and vexing neurodevelopmental disorders among children. Although the two disorders share many behavioral and neuropsychological characteristics, most MRI studies examine only one of the disorders at a time. Using graph theory combined with structural and functional connectivity, we examined the large-scale network organization among three groups of children: a group with ADHD (8-12 years, n = 20), a group with ASD (7-13 years, n = 16), and typically developing controls (TD) (8-12 years, n = 20). We apply the concept of the rich-club organization, whereby central, highly connected hub regions are also highly connected to themselves. We examine the brain into two different network domains: (1) inside a rich-club network phenomena and (2) outside a rich-club network phenomena. The ASD and ADHD groups had markedly different patterns of rich club and non rich-club connections in both functional and structural data. The ASD group exhibited higher connectivity in structural and functional networks but only inside the rich-club networks. These findings were replicated using the autism brain imaging data exchange dataset with ASD (n = 85) and TD (n = 101). The ADHD group exhibited a lower generalized fractional anisotropy and functional connectivity inside the rich-club networks, but a higher number of axonal fibers and correlation coefficient values outside the rich club. Despite some shared biological features and frequent comorbity, these data suggest ADHD and ASD exhibit distinct large-scale connectivity patterns in middle childhood. Hum Brain Mapp, 2014. (c) 2014 Wiley Periodicals, Inc.

Recht, M., Neufeld, E. J., Sharma, V. R., Solem, C. T., Pickard, A. S., Gut, R. Z., et al. (2014). Impact of acute bleeding on daily activities of patients with congenital hemophilia with inhibitors and their caregivers and families: Observations from the dosing observational study in hemophilia (DOSE). *Value in Health,*

Objectives: There is limited understanding of the effects of bleeding episodes on the daily lives of patients with congenital hemophilia with inhibitors and their caregivers. This analysis of the Dosing Observational Study in Hemophilia examined the impact of acute bleeding episodes on work, school, and family activities. Methods: Patients and caregivers participated in a diary study for 90 or more days or until patients experienced four bleeding episodes. All bleed treatments, interference with daily activities, and quality-of-life assessments were captured in daily records. Patients and caregivers reported planned workdays or school days eligible to be "lost" so as to differentiate from days lost because of disability or nonworking status, weekends, and vacations. Results: Diaries were completed for 39 patients (18 adults and 21 children). Bleeding episodes that continued for 3 or more days (16.4%) accounted for most of the major changes to family plans. For the 38 patients with bleeding episodes, 47% of 491 bleed days fell on planned workdays or school days; the remainder fell on weekends, holidays, or nonworkdays or non-school days and therefore did not count as "lost days." Patients reported a loss of productivity on a greater percentage of eligible bleed days than did caregivers (3.9% vs. 0.8%, respectively). Patients and caregivers reported 13.5%/9.3% fully missed and 3.5%/7.6% partially missed days. Conclusions: This study demonstrated that in hemophilia with inhibitors, bleeding episodes interfere with the daily activities of patients and their caregivers. Furthermore, documenting only lost days underestimated the impact of bleeding episodes because of the high percentage of days without planned work or school.

Ren, T., He, W., Li, Y., Grosh, K., & Fridberger, A. (2014). Light-induced vibration in the hearing organ. *Scientific Reports, 4*, 5941.

The exceptional sensitivity of mammalian hearing organs is attributed to an active process, where force produced by sensory cells boost sound-induced vibrations, making soft sounds audible. This process is thought to be local, with each section of the hearing organ capable of amplifying sound-evoked movement, and nearly instantaneous, since amplification can work for sounds at frequencies up to 100 kHz in some species. To test these fundamental precepts, we developed a method for focally stimulating the living hearing organ with light. Light pulses caused intense and highly damped mechanical responses followed by traveling waves that developed with

considerable delay. The delayed response was identical to movements evoked by click-like sounds. This shows that the active process is neither local nor instantaneous, but requires mechanical waves traveling from the cochlear base toward its apex. A physiologically-based mathematical model shows that such waves engage the active process, enhancing hearing sensitivity.

Rescorla, L. A., Bochicchio, L., Achenbach, T. M., Ivanova, M. Y., Almqvist, F., Begovac, I., et al. (2014). Parent-teacher agreement on children's problems in 21 societies. *Journal of Clinical Child and Adolescent Psychology, 43*(4), 627-642.

Parent-teacher cross-informant agreement, although usually modest, may provide important clinical information. Using data for 27,962 children from 21 societies, we asked the following: (a) Do parents report more problems than teachers, and does this vary by society, age, gender, or type of problem? (b) Does parent-teacher agreement vary across different problem scales or across societies? (c) How well do parents and teachers in different societies agree on problem item ratings? (d) How much do parent-teacher dyads in different societies vary in within-dyad agreement on problem items? (e) How well do parents and teachers in 21 societies agree on whether the child's problem level exceeds a deviance threshold? We used five methods to test agreement for Child Behavior Checklist (CBCL) and Teacher's Report Form (TRF) ratings. CBCL scores were higher than TRF scores on most scales, but the informant differences varied in magnitude across the societies studied. Cross-informant correlations for problem scale scores varied moderately across societies studied and were significantly higher for Externalizing than Internalizing problems. Parents and teachers tended to rate the same items as low, medium, or high, but within-dyad item agreement varied widely in every society studied. In all societies studied, both parental noncorroboration of teacher-reported deviance and teacher noncorroboration of parent-reported deviance were common. Our findings underscore the importance of obtaining information from parents and teachers when evaluating and treating children, highlight the need to use multiple methods of quantifying cross-informant agreement, and provide comprehensive baselines for patterns of parent-teacher agreement across 21 societies.

Riddle, M. C., Bolli, G. B., Ziemen, M., Muehlen-Bartmer, I., Bizet, F., Home, P. D., et al. (2014). New insulin glargine 300 Units/mL versus glargine 100 Units/mL in people with type 2 diabetes using basal and mealtime insulin: Glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care,*

OBJECTIVE: To compare the efficacy and safety of new insulin glargine 300 units/mL (Gla-300) with glargine 100 units/mL (Gla-100) in people with type 2 diabetes on basal insulin (>/=42 units/day) plus mealtime insulin. RESEARCH DESIGN AND METHODS: EDITION 1 (NCT01499082) was a 6-month, multinational, open-label, parallel-group study. Adults with glycated hemoglobin A1c (HbA1c) 7.0-10.0% (53-86 mmol/mol) were randomized to Gla-300 or Gla-100 once daily with dose titration seeking fasting plasma glucose 4.4-5.6 mmol/L. Primary end point was HbA1c change from baseline; main secondary end point was percentage of participants with one or more confirmed (</=3.9 mmol/L) or severe nocturnal hypoglycemia from week 9 to month 6. RESULTS: Participants (n = 807) had mean age 60 years, diabetes duration 16 years, BMI 36.6 kg/m2, and HbA1c 65.6 mmol/mol (8.15%). HbA1c reduction was equivalent between regimens; least squares mean difference -0.00% (95% CI -0.11 to 0.11) (-0.00 mmol/mol [-1.2 to 1.2]). Fewer participants reported one or more confirmed (</=3.9 mmol/L) or severe nocturnal hypoglycemic events between week 9 and month 6 with Gla-300 (36 vs. 46% with Gla-100; relative risk 0.79 [95% CI 0.67-0.93]; P < 0.005); nocturnal hypoglycemia incidence and event rates were also lower with Gla-300 in the first 8 weeks of treatment. No between-treatment differences in tolerability or safety were identified. CONCLUSIONS: Gla-300 controls HbA1c as well as Gla-100 for people with type 2 diabetes treated with basal and mealtime insulin, but with consistently less risk of nocturnal hypoglycemia.

Rodriguez, M. I., Evans, M., & Espey, E. (2014). Advocating for immediate postpartum LARC: Increasing access, improving outcomes, and decreasing cost. *Contraception,*

Roh, J. I., Cheong, C., Sung, Y. H., Lee, J., Oh, J., Lee, B. S., et al. (2014). Perturbation of NCOA6 leads to dilated cardiomyopathy. *Cell Reports, 8*(4), 991-998.

Dilated cardiomyopathy (DCM) is a progressive heart disease characterized by left ventricular dilation and contractile dysfunction. Although many candidate genes have been identified with

mouse models, few of them have been shown to be associated with DCM in humans. Germline depletion of Ncoa6, a nuclear hormone receptor coactivator, leads to embryonic lethality and heart defects. However, it is unclear whether Ncoa6 mutations cause heart diseases in adults. Here, we report that two independent mouse models of NCOA6 dysfunction develop severe DCM with impaired mitochondrial function and reduced activity of peroxisome proliferator-activated receptor delta (PPARdelta), an NCOA6 target critical for normal heart function. Sequencing of NCOA6-coding regions revealed three independent nonsynonymous mutations present in 5 of 50 (10%) patients with idiopathic DCM (iDCM). These data suggest that malfunction of NCOA6 can cause DCM in humans.

Rønnekleiv, O. K., Fang, Y., Zhang, C., Nestor, C. C., Mao, P., & Kelly, M. J. (2014). Research resource: Gene profiling of G protein-coupled receptors in the arcuate nucleus of the female. *Molecular Endocrinology, 28*(8), 1362-1380.

The hypothalamic arcuate nucleus controls many critical homeostatic functions including energy homeostasis, reproduction, and motivated behavior. Although G protein-coupled receptors (GPCRs) are involved in the regulation of these functions, relatively few of the GPCRs have been identified specifically within the arcuate nucleus. Here, using TaqMan low-density arrays we quantified the mRNA expression of nonolfactory GPCRs in mouse arcuate nucleus. An unprecedented number of GPCRs (total of 292) were found to be expressed, of which 183 were known and 109 were orphan GPCRs. The known GPCR genes expressed were classified into several functional clusters including hormone/neurotransmitter, growth factor, angiogenesis and vasoactivity, inflammation and immune system, and lipid messenger receptors. The plethora of orphan genes expressed in the arcuate nucleus were classified into 5 structure-related classes including class A (rhodopsin-like), class B (adhesion), class C (other GPCRs), nonsignaling 7-transmembrane chemokine- binding proteins, and other 7-transmembrane proteins. Therefore, for the first time, we provide a quantitative estimate of the numerous GPCRs expressed in the hypothalamic arcuate nucleus. Finally, as proof of principle, we documented the expression and function of one of these receptor genes, the glucagon-like peptide 1 receptor (Glp1r), which was highly expressed in the arcuate nucleus. Single-cell RT-PCR revealed that Glp1r mRNA was localized in proopiomelanocortin neurons, and using whole-cell recording we found that the

glucagon-like peptide 1-selective agonist exendin-4 robustly excited proopiomelanocortin neurons. Thus, the quantitative GPCR data emphasize the complexity of the hypothalamic arcuate nucleus and furthermore provide a valuable resource for future neuroendocrine/endocrine-related experiments. © 2014 by the Endocrine Society.

Ross, D. A. (2014). Complications of minimally invasive, tubular access surgery for cervical, thoracic, and lumbar surgery. *Minimally Invasive Surgery, 2014*, 451637.

The object of the study was to review the author's large series of minimally invasive spine surgeries for complication rates. The author reviewed a personal operative database for minimally access spine surgeries done through nonexpandable tubular retractors for extradural, nonfusion procedures. Consecutive cases (n = 1231) were reviewed for complications. There were no wound infections. Durotomy occurred in 33 cases (2.7% overall or 3.4% of lumbar cases). There were no external or symptomatic internal cerebrospinal fluid leaks or pseudomeningoceles requiring additional treatment. The only motor injuries were 3 C5 root palsies, 2 of which resolved. Minimally invasive spine surgery performed through tubular retractors can result in a low wound infection rate when compared to open surgery. Durotomy is no more common than open procedures and does not often result in the need for secondary procedures. New neurologic deficits are uncommon, with most observed at the C5 root. Minimally invasive spine surgery, even without benefits such as less pain or shorter hospital stays, can result in considerably lower complication rates than open surgery.

Rudmik, L., & Smith, T. L. (2014). Economic evaluation of a steroid-eluting sinus implant following endoscopic sinus surgery for chronic rhinosinusitis. *Otolaryngology - Head and Neck Surgery (United States), 151*(2), 359-366.

Objective. This study aimed to evaluate the cost-effectiveness of a mometasone steroid-eluting sinus implant compared to a nonsteroid-eluting sinus implant following endoscopic sinus surgery (ESS) for chronic rhinosinusitis. Study Design. Economic evaluation using a decision tree model. Setting. Academic and nonacademic otolaryngology practices. Subjects. Patients with refractory chronic rhinosinusitis undergoing ESS. Methods. The economic perspective was the health care third party payer. Effectiveness and probability data were obtained from a single meta-analysis of

2 randomized, double-blind, controlled trials. Costs were obtained from the Centers for Medicare & Medicaid Services database and wholesale pharmaceutical pricing. Multiple sensitivity analyses were performed including a probabilistic sensitivity analysis. Comparative treatment groups were (1) placement of the mometasone steroid-eluting sinus implant following ESS and (2) placement of a nonsteroid-eluting implant following ESS. The primary outcome was cost per postoperative intervention avoided within 60 days after ESS. Results. The mean cost for the steroid-eluting and nonsteroideluting sinus implant strategies were $1,572.91 and $365.18, respectively. The steroid-eluting strategy incremental costeffectiveness ratio was $5,489.68. The sensitivity analysis demonstrated a 74.3%, 87.2%, and 90.5% certainty that the steroideluting implant strategy is cost-effective at willingness-to-pay thresholds of $10,000, $25,000, and $50,000, respectively. Conclusion. Results from this economic evaluation suggest that placement of a mometasone steroid-eluting sinus implant into the ethmoid cavity following ESS for refractory chronic rhinosinusitis is a cost-effective intervention for preventing a postoperative intervention within 60 days after surgery. © American Academy of OtolaryngologyHead and Neck Surgery Foundation 2014.

Saharan, S., Legg, A. T., Armsby, L. B., Zubair, M. M., Reed, R. D., & Langley, S. M. (2014). Causes of readmission after operation for congenital heart disease. *The Annals of Thoracic Surgery,* BACKGROUND: Readmission after operations for congenital heart conditions has significant implications for patient care. Readmission rates vary between 8.7% and 15 %. The aim of this study was to determine the incidence, causes, and risk factors associated with readmission. METHODS: 811 consecutive patients undergoing operations for congenital heart conditions were analyzed. Readmission was defined as admission to any hospital within 30 days of discharge for any cause. Demographic, preoperative, operative, and postoperative variables were evaluated. Univariate comparisons were made between the nonreadmission and readmission groups, and multivariate logistic regression analysis was made to determine independent risk factors for readmission. RESULTS: There were a total of 92 readmissions in 79 patients (9.7%). The reasons included cardiac (36, 39%), pulmonary (20, 22%), gastrointestinal (13, 14%), infectious (20, 22%), and other adverse events (2, 2%). Patients with either single-ventricle palliation or nasogastric feeding accounted for 40 (50%) readmissions. On univariate analysis, there were

significant differences between readmitted and nonreadmitted patients in relation to patient age, chromosomal abnormality, mortality risk score, duration of mechanical ventilation, postoperative length of stay, single-ventricle physiology, and nasogastric feeding at discharge ($p < 0.05$). On multivariate analysis, significant risk factors for readmission were single-ventricle physiology (odds ratio [OR] 2.39; 95% confidence interval [CI] 1.28 to 4.47; $p = 0.005$), preoperative arrhythmia (OR 2.59; 95% CI 1.02 to 6.59; $p = 0.04$), longer postoperative length of stay (OR 2.2; 95% CI 1.22 to 3.99; $p = 0.008$), and nasogastric tube feeding at discharge (OR 2.2; 95% CI 1.15 to 4.19; $p = 0.01$). CONCLUSIONS: The incidence of readmission after operations for congenital cardiac conditions remains high. Efforts focusing on patients with single-ventricle palliation and those with preoperative arrhythmia, prolonged postoperative length of stay and nasogastric tube feeding at discharge may be particularly beneficial.

Saitz, T. R., & Serefoglu, E. C. (2014). Gene mapping of serotoninergic system polymorphisms provides insight on pathology and treatment of men with lifelong premature ejaculation. *Asian Journal of Andrology, 16*(4), 643.

Samuels, M. H. (2014). Psychiatric and cognitive manifestations of hypothyroidism. *Current Opinion in Endocrinology, Diabetes, and Obesity, 21*(5), 377-383.

PURPOSE OF REVIEW: Overt hypothyroidism has major effects on neuropsychiatric function, but patients with mild hypothyroidism may attribute unrelated neuropsychiatric symptoms to their thyroid condition. This review will summarize data on neuropsychiatric effects of hypothyroidism, and provide guidelines regarding the relationship between hypothyroidism and neuropsychiatric issues, and treatment indications. RECENT FINDINGS: Clinical investigations and functional imaging studies confirm that overt hypothyroidism is associated with affective and cognitive decrements, largely reversible with treatment. In contrast, subclinical hypothyroidism is not associated with major neuropsychiatric deficits, although studies utilizing sensitive measures show small deficits in memory and executive function. Neuropsychiatric complaints are more common when patients are aware of their thyroid disease, regardless of their thyroid function at the time of testing. SUMMARY: Neuropsychiatric dysfunction is common in overt hypothyroidism and will improve (perhaps not completely resolve) with therapy. Deficits related to thyroid

dysfunction are usually mild in subclinical hypothyroidism, and realistic expectations need to be set regarding symptom reversibility with treatment. Patients with mild hypothyroidism and significant distress related to neuropsychiatric symptoms, most likely, have independent diagnoses that should be evaluated separately.

Sandner, F., Welter, H., Schwarzer, J. U., Köhn, F. M., Urbanski, H. F., & Mayerhofer, A. (2014). Expression of the oestrogen receptor GPER by testicular peritubular cells is linked to sexual maturation and male fertility. *Andrology, 2*(5), 695-701.

Besides the two nuclear oestrogen receptors (ESR1/ESR2), the G protein-coupled oestrogen receptor (GPER) was described in the human testis but little is known about testicular GPER during development or male infertility. We performed an immunohistochemical analysis using human and rhesus monkey testicular samples. The results obtained in adult primate testes showed GPER in interstitial and vascular cells as well as in smooth muscle-like peritubular cells, which build the wall of seminiferous tubules. Expression of GPER was also found in cultured human testicular peritubular cells (HPTCs) by Western blotting and RT-PCR/sequencing. Furthermore, as seen in time-lapse videos of cultured cells, addition of a specific GPER agonist (G1) significantly reduced the numbers of HTPCs within 24 h. A GPER antagonist (G15) prevented this action, implying a role for GPER related to the control of cell proliferation or cell death of peritubular cells. Peritubular cell functions and their phenotype change, for example, during post-natal development and in the cases of male infertility. The study of non-human primate samples revealed that GPER in peritubular cells was detectable only from the time of puberty onwards, while in samples from infantile and prepubertal monkeys only interstitial cells showed immunopositive staining. In testicular biopsies of men with mixed atrophy, a reduction or loss of immunoreactive GPER was found in peritubular cells surrounding those tubules, in which spermatogenesis was impaired. In other cases of impaired spermatogenesis, namely when the tubular wall was fibrotically remodelled, a complete loss of GPER was seen. Thus, the observed inverse relation between the state of fertility and GPER expression by peritubular cells implies that the regulation of primate testicular peritubular cells by oestrogens is mediated by GPER in both, health and disease.

Sather, D. N., Carbonetti, S., Malherbe, D., Pissani, F., Stuart, A. B., Hessell, A. J., et al. (2014). Emergence of broadly neutralizing antibodies and viral co-evolution in two subjects during the early stages of infection with the human immunodeficiency virus type 1. *Journal of Virology,* Delineating the key early events that lead to the development of broadly neutralizing anti-HIV-1 antibodies during natural infection may help guide the development of immunogens and vaccine regimens to prevent HIV-1 infection. In this study, we followed two HIV-1 positive subjects, VC20013 and VC10014, over the course of infection from before they developed broadly neutralizing antibody (bNAb) activity until several years after breadth was detected in the plasma. Both subjects developed bNAb activity after approximately one year post infection, which ultimately mapped to the membrane proximal external region (MPER) in VC20013 and an epitope that overlaps the CD4 receptor binding site in VC10014. In subject VC20013, we were able to identify anti-MPER activity in the earliest plasma sample that exhibited no bNAb activity, indicating that this epitope specificity was acquired very early on, but that it was initially not able to mediate neutralization. Escape mutations within the bNAb epitopes did not arise in the circulating envelopes until bNAb activity was detectable in the plasma, indicating that this early response was not sufficient to drive viral escape. As bNAb activity began to emerge in both subjects, we observed a simultaneous increase in autologous anti-Envelope antibody binding affinity, indicating that antibody maturation was occurring as breadth was developing. Our findings illustrate one potential mechanism by which bNAbs develop during natural infection in which an epitope target is acquired very early on during the course of infection, but requires time and maturation to develop into broadly neutralizing activity. IMPORTANCE: One major goal of HIV-1 vaccine research is the development of a vaccine that can elicit broadly neutralizing antibodies (bNAbs). Although no such vaccine exists, bNAbs develop in approximately twenty percent of HIV-1-infected subjects, providing prototype of the bNAbs that must be re-elicited by vaccine. Thus, there is significant interest in understanding the mechanisms by which bNAbs develop during the course of infection. We studied the timing, the epitope specificity, and the evolution of the bNAb responses in two HIV-1 positive patients who developed bNAb activity within the first several years after infection. In one subject, antibodies to a broadly neutralizing epitope developed very early but were non-neutralizing. After several months neutralizing activity developed and the virus mutated to escape their activity. Our study highlights one mechanism for

the development of bNAbs where early epitope acquisition followed by sufficient time for antibody maturation drives the epitope-specific antibody response toward broadly neutralizing activity.

Saultz, J. (2014). Safety first. *Family Medicine, 46*(8), 585-586.

Saunders, G. H., Frederick, M. T., Chisolm, T. H., Silverman, S., Arnold, M., & Myers, P. (2014). Use of a frequency-modulated system for veterans with blast exposure, perceived hearing problems, and normal hearing sensitivity. *Seminars in Hearing, 35*(3), 227-238.

Traumatic brain injury can impact the central auditory system leading to poor auditory recall and increased difficulties hearing in poor acoustic environments. In recent years, audiologists have increasingly encountered blast-exposed veterans who report speech understanding problems that are disproportionate to their essentially normal hearing sensitivity, and thus are thought to have an auditory processing disorder. In light of studies showing frequency-modulated (FM) systems to be effective rehabilitation for auditory processing difficulties, we examined the use of an FM system intervention for blast-exposed veterans with functional hearing problems in the presence of normal hearing sensitivity. The outcomes for three veterans who were provided with an FM system as part of a multisite randomized clinical trial are described. Data indicate that FM systems are beneficial for some patients reporting hearing problems in the presence of normal hearing sensitivity but factors other than audiometric profile and reported complaints influence outcome. These include understanding of speech in noise, patient communication demands, auditory lifestyle, and the presence of posttraumatic stress disorder or other mental health factors. Furthermore, education (and reeducation if necessary) of the patient and their spouse or family is critical to successful outcome. © 2014 by Thieme Medical Publishers, Inc.

Saute, J. A., Giugliani, R., Merkens, L. S., Chiang, J., DeBarber, A. E., & de Souza, C. F. M. (2014). Look carefully to the heels! A potentially treatable cause of spastic paraplegia. *Journal of Inherited Metabolic Disease,*

? © 2014 SSIEM.

Schreiber, M. A. (2014). Is any test 100% specific and 100% sensitive for serious injury? *JAMA Surgery,*

Schulman, P., Gelow, J., Matthias, M., Mudd, J., Wei, K., & Hutchens, M. (2014). Critical care transthoracic echocardiography: Atrial sinus rhythm during ventricular fibrillation. *Journal of Investigative Medicine High Impact Case Reports, 2*(1), 10.1177/2324709614524945.

Shapiro, M. D., & Cigarroa, J. E. (2014). Coronary CT angiography-A rosetta stone for understanding and treating bifurcation lesions? *Catheterization and Cardiovascular Interventions : Official Journal of the Society for Cardiac Angiography & Interventions, 84*(3), 453-454.

Simianu, V. V., Bastawrous, A. L., Billingham, R. P., Farrokhi, E. T., Fichera, A., Herzig, D. O., et al. (2014). Addressing the appropriateness of elective colon resection for diverticulitis: A report from the SCOAP CERTAIN collaborative. *Annals of Surgery, 260*(3), 533-539.
OBJECTIVE: To assess the reported indications for elective colon resection for diverticulitis and concordance with professional guidelines. BACKGROUND: Despite modern professional guidelines recommending delay in elective colon resection beyond 2 episodes of uncomplicated diverticulitis, the incidence of elective colectomy has increased dramatically in the last 2 decades. Whether surgeons have changed their threshold for recommending a surgical intervention is unknown. In 2010, Washington State's Surgical Care and Outcomes Assessment Program initiated a benchmarking and education initiative related to the indications for colon resection. METHODS: Prospective cohort study evaluating indications from chronic complications (fistula, stricture, bleeding) or the number of previously treated diverticulitis episodes for patients undergoing elective colectomy at 1 of 49 participating hospitals (2010-2013). RESULTS: Among 2724 patients (58.7 +/- 13 years; 46% men), 29.4% had a chronic complication indication (15.6% fistula, 7.4% stricture, 3.0% bleeding, 5.8% other). For the 70.5% with an episode-based indication, 39.4% had 2 or fewer episodes, 56.5% had 3 to 10 episodes, and 4.1% had more than 10 episodes. Thirty-one percent of patients failed to meet indications for either a chronic complication or 3 or more episodes. Over the 4 years, the proportion of patients with an indication of 3 or more episodes increased from 36.6% to 52.7% ($P < 0.001$) whereas the proportion of those who failed to meet either clinical or episode-based indications decreased from 38.4% to 26.4% ($P < 0.001$). The annual rate of emergency resections did not increase significantly, varying from 5.6 to 5.9 per year ($P = 0.81$). CONCLUSIONS: Adherence to a

guideline based on 3 or more episodes for elective colectomy increased concurrently with a benchmarking and peer-to-peer messaging initiative. Improving adherence to professional guidelines related to appropriate care is critical and can be facilitated by quality improvement collaboratives.

Smith, J. S., Singh, M., Klineberg, E., Shaffrey, C. I., Lafage, V., Schwab, F. J., et al. (2014). Surgical treatment of pathological loss of lumbar lordosis (flatback) in patients with normal sagittal vertical axis achieves similar clinical improvement as surgical treatment of elevated sagittal vertical axis: Clinical article. *Journal of Neurosurgery: Spine, 21*(2), 160-170.

Object. Increased sagittal vertical axis (SVA) correlates strongly with pain and disability for adults with spinal deformity. A subset of patients with sagittal spinopelvic malalignment (SSM) have flatback deformity (pelvic incidence-lumbar lordosis [PI-LL] mismatch > 10°) but remain sagittally compensated with normal SVA. Few data exist for SSM patients with flatback deformity and normal SVA. The authors' objective was to compare baseline disability and treatment outcomes for patients with compensated (SVA 10°) and decompensated (SVA > 5 cm) SSM. Methods. The study was a multicenter, prospective analysis of adults with spinal deformity who consecutively underwent surgical treatment for SSM. Inclusion criteria included age older than 18 years, presence of adult spinal deformity with SSM, plan for surgical treatment, and minimum 1-year follow-up data. Patients with SSM were divided into 2 groups: those with compensated SSM (SVA 10°) and those with decompensated SSM (SVA ≥ 5 cm). Baseline and 1-year follow-up radiographic and health-related quality of life (HRQOL) outcomes included Oswestry Disability Index, Short Form-36 scores, and Scoliosis Research Society-22 scores. Percentages of patients achieving minimal clinically important difference (MCID) were also assessed. Results. A total of 125 patients (27 compensated and 98 decompensated) met inclusion criteria. Compared with patients in the compensated group, patients in the decompensated group were older (62.9 vs 55.1 years; $p = 0.004$) and had less scoliosis (43° vs 54°; $p = 0.002$), greater SVA (12.0 cm vs 1.7 cm; $p < 0.001$), greater PI-LL mismatch (26° vs 20°; $p = 0.013$), and poorer HRQOL scores (Oswestry Disability Index, Short Form-36 physical component score, Scoliosis Research Society-22 total; $p \leq 0.016$). Although these baseline HRQOL differences between the groups reached statistical significance, only the mean difference in Short Form-36 physical component score

reached threshold for MCID. Compared with baseline assessment, at 1 year after surgery improvement was noted for patients in both groups for mean SVA (compensated -1.1 cm, decompensated +4.8 cm; $p \leq 0.009$), mean PI-LL mismatch (compensated 6°, decompensated 5°; $p < 0.001$), and all HRQOL measures assessed ($p \leq 0.005$). No significant differences were found between the compensated and decompensated groups in the magnitude of HRQOL score improvement or in the percentages of patients achieving MCID for each of the outcome measures assessed. Conclusions. Decompensated SSM patients with elevated SVA experience significant disability; however, the amount of disability in compensated SSM patients with flatback deformity caused by PI-LL mismatch but normal SVA is underappreciated. Surgical correction of SSM demonstrated similar radiographic and HRQOL score improvements for patients in both groups. Evaluation of SSM should extend beyond measuring SVA. Among patients with concordant pain and disability, PI-LL mismatch must be evaluated for SSM patients and can be considered a primary indication for surgery.

Smith, K. A., Harvath, T. A., Goy, E. R., & Ganzini, L. (2014). Predictors of pursuit of physician-assisted death. *Journal of Pain and Symptom Management,*

CONTEXT: Physician-assisted death (PAD) was legalized in 1997 by Oregon's Death with Dignity Act (DWDA). The States of Washington, Montana, and Vermont have since provided legal sanction for PAD. Through 2013, 1173 Oregonians have received a prescription under the DWDA and 752 have died after taking the prescribed medication in Oregon. OBJECTIVES: To determine the predictive value of personal and interpersonal variables in the pursuit of PAD. METHODS: Fifty-five Oregonians who either requested PAD or contacted a PAD advocacy organization were compared with 39 individuals with advanced disease who did not pursue PAD. We compared the two groups on responses to standardized measures of depression, hopelessness, spirituality, social support, and pain. We also compared the two groups on style of attachment to intimate others and caregivers as understood through attachment theory. RESULTS: We found that PAD requesters had higher levels of depression, hopelessness, and dismissive attachment (attachment to others characterized by independence and self-reliance), and lower levels of spirituality. There were moderate correlations among the variables of spirituality, hopelessness, depression, social support, and dismissive attachment. There was a strong correlation between depression and

hopelessness. Low spirituality emerged as the strongest predictor of pursuit of PAD in the regression analysis. CONCLUSION: Although some factors motivating pursuit of PAD, such as depression, may be ameliorated by medical interventions, other factors, such as style of attachment and sense of spirituality, are long standing aspects of the individual that should be supported at the end of life. Practitioners must develop respectful awareness and understanding of the interpersonal and spiritual perspectives of their patients in order to provide such support.

Smith, L. B., Kugler, B. B., Lewin, A. B., Duke, D. C., Storch, E. A., & Geffken, G. R. (2014). Executive functioning, parenting stress, and family factors as predictors of diabetes management in pediatric patients with type 1 diabetes using intensive regimens. *Children's Health Care, 43*(3), 234-252.

The care of youth with type 1 diabetes mellitus (T1DM) has become increasingly complex given the importance of good glycemic control in decreasing the rates of diabetes-related complications. Today, youth with TIDM are more frequently prescribed intensive insulin regimens (i.e. multiple daily injections or insulin pump therapy) which require a great deal of planning, organization, and problem-solving to execute correctly. However, there has been a paucity of research on psychological and family factors that may impact pediatric patients diabetes management when using intensive regimens. Seventy-two youth with T1DM on intensive insulin regimens and their caregivers participated in the study, which entailed completing self-report questionnaires, an adherence interview, a parent-report measure of executive functioning, and measurement of glycemic control. Results suggested that although adherence mediated the relation between child executive functioning and glycemic control in youth reporting relatively better adherence, this finding was not supported in youth reporting relatively worse adherence. Regression models including all study variables accounted for large proportions of the variance in glycemic control, although there were differences based on child-reported adherence. Findings from this study provide preliminary information about characteristics associated with outcome for youth with T1DM utilizing intensive insulin regimens.

Smith, T. L., & Sautter, N. B. (2014). Is montelukast indicated for treatment of chronic rhinosinusitis with polyposis? *Laryngoscope, 124*(8), 1735-1736.

Sorror, M. L., Storb, R. F., Sandmaier, B. M., Maziarz, R. T., Pulsipher, M. A., Maris, M. B., et al. (2014). Comorbidity-age index: A clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,*

PURPOSE: Age has long been used as a major factor for assessing suitability for allogeneic hematopoietic cell transplantation (HCT). The HCT-comorbidity index (HCT-CI) was developed as a measure of health status to predict mortality risk after HCT. Whether age, comorbidities, or both should guide decision making for HCT is unknown. PATIENTS AND METHODS: Data from 3,033 consecutive recipients of HLA-matched grafts from five institutions contributed to this analysis. Patients were randomly divided into a training set to develop weights for age intervals and a validation set to assess the performance of prognostic models. RESULTS: In the training set, patients age 20 to 39 years, 40 to 49 years, 50 to 59 years, and >/= 60 years had hazard ratios for nonrelapse mortality (NRM) of 1.21 (P = .29), 1.48 (P = .04), 1.75 (P = .004), and 1.84 (P = .005), respectively, compared with those age younger than 20 years. Consequently, age >/= 40 years was assigned a weight of 1 to be added to the HCT-CI to constitute a composite comorbidity/age index. In the validation set, the composite comorbidity/age score had statistically significantly higher c-statistic estimates for prediction of NRM (0.664 v 0.556; P /= 5 had statistically significant higher mortality risks after high-dose versus nonmyeloablative regimens. CONCLUSION: Age is a poor prognostic factor. The proposed composite measure allows integration of both comorbidities and age into clinical decision making and comparative-effectiveness research of HCT.

Spellberg, B., & Gilbert, D. N. (2014). The future of antibiotics and resistance: A tribute to a career of leadership by john bartlett. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America, 59 Suppl 2*, S71-5.

The ways we have developed, used, and protected antibiotics have led, predictably, to our current crisis of rising antibiotic resistance and declining new treatments. If we want to stave off a postantibiotic era, we need to fundamentally change our approach. We need to challenge long-standing assumptions and cherished beliefs. We need to push through the reflexive resistance and excuses (eg, "that's not how we do things" and "that can't be done") that result from

challenging established ways. Excuses abound. Action is needed. Ultimately, we need a coordinated national action plan to combat resistance. Herein we discuss 7 tasks and 3 common themes that cut across those tasks, which are necessary to achieve long-term success in dealing with antibiotics and resistance. These principles derive from many years of dialogue with Dr John Bartlett. The field of infectious diseases, and indeed medicine in general, has benefited immeasurably from his remarkable leadership.

Stain, S. C., Hoyt, D. B., Hunter, J. G., Joyce, G., & Hiatt, J. R. (2014). American surgery and the affordable care act. *JAMA Surgery,*

The Affordable Care Act (ACA) attempts to change the way we finance and deliver health care by coordinating the delivery of primary, specialty, and hospital services in accountable care organizations. The ways in which accountable care organizations will develop and evolve is unclear; however, the effects on surgeons and their patients will be substantial. High-value care in the ACA emphasizes quality, safety, resource use and appropriateness, and the patient's experience of care. Payment will be linked to these principles. Department chairs overseeing a clinical enterprise in academic medical centers now must add financial and quality measures to the traditional missions of education, research, and clinical service. At a time when surgical training is in dramatic evolution, with work hour limitations for residents and an emphasis on quality, productivity, and increasing oversight of trainees for faculty, residency programs will need to meet the increasing demands of an aging population and newly insured patients under the ACA. The American College of Surgeons, with its century-long commitment to quality improvement, research-based standards, and performance measurement and verification, has begun its Inspiring Quality Campaign, is developing new educational tools, and is preparing proposals for payment reform based on surgeons' participation in quality programs.

Stecker, E. C. (2014). A nonshocking new way to prevent sudden death. *Science Translational Medicine, 6*(243)

Sun, B. C., McCreath, H., Liang, L. -., Bohan, S., Baugh, C., Ragsdale, L., et al. (2014). Randomized clinical trial of an emergency department observation syncope protocol versus routine inpatient admission. *Annals of Emergency Medicine, 64*(2), 167-175.

Study objective Older adults are frequently hospitalized from the emergency department (ED) after an episode of unexplained syncope. Current admission patterns are costly, with little evidence of benefit. We hypothesize that an ED observation syncope protocol will reduce resource use without adversely affecting patient-oriented outcomes. Methods This randomized trial at 5 EDs compared an ED observation syncope protocol to inpatient admission for intermediate-risk adults (≥50 years) presenting with syncope or near syncope. Primary outcomes included inpatient admission rate and length of stay. Secondary outcomes included 30-day and 6-month serious outcomes after hospital discharge, index and 30-day hospital costs, 30-day quality-of-life scores, and 30-day patient satisfaction. Results Study staff randomized 124 patients. Observation resulted in a lower inpatient admission rate (15% versus 92%; 95% confidence interval [CI] difference -88% to -66%) and shorter hospital length of stay (29 versus 47 hours; 95% CI difference -28 to -8). Serious outcome rates after hospital discharge were similar for observation versus admission at 30 days (3% versus 0%; 95% CI difference -1% to 8%) and 6 months (8% versus 10%; 95% CI difference -13% to 9%). Index hospital costs in the observation group were $629 (95% CI difference -$1,376 to -$56) lower than in the admission group. There were no differences in 30-day quality-of-life scores or in patient satisfaction. Conclusion An ED observation syncope protocol reduced the primary outcomes of admission rate and hospital length of stay. Analyses of secondary outcomes suggest reduction in index hospital costs, with no difference in safety events, quality of life, or patient satisfaction. Our findings suggest that an ED observation syncope protocol can be replicated and safely reduce resource use.

Svalina, M. N., & Keller, C. (2014). YAPping about differentiation therapy in muscle cancer. *Cancer Cell, 26*(2), 154-155.

Overcoming a presumed differentiation block in the childhood muscle cancer embryonal rhabdomyosarcoma is often thought to hold promise as an approach to replace cytotoxic chemotherapy with molecularly-targeted differentiation therapies. In this issue of Cancer Cell, Tremblay and colleagues implicate YAP1 and the Hippo signaling pathway in the maintenance of differentiation-arrested and proliferative phenotypes for embryonal rhabdomyosarcoma.

Swartz, C. M. (2014). Artifactual effect of propofol on ECT peak heart rate. *Psychiatry Research,*

Tanaka, C., Nguyen-Huynh, A., Loera, K., Stark, G., & Reiss, L. (2014). Factors associated with hearing loss in a normal-hearing guinea pig model of hybrid cochlear implants. *Hearing Research, 316C*, 82-93.

The Hybrid cochlear implant (CI), also known as Electro-Acoustic Stimulation (EAS), is a new type of CI that preserves residual acoustic hearing and enables combined cochlear implant and hearing aid use in the same ear. However, 30-55% of patients experience acoustic hearing loss within days to months after activation, suggesting that both surgical trauma and electrical stimulation may cause hearing loss. The goals of this study were to: 1) determine the contributions of both implantation surgery and EAS to hearing loss in a normal-hearing guinea pig model; 2) determine which cochlear structural changes are associated with hearing loss after surgery and EAS. Two groups of animals were implanted (n = 6 per group), with one group receiving chronic acoustic and electric stimulation for 10 weeks, and the other group receiving no direct acoustic or electric stimulation during this time frame. A third group (n = 6) was not implanted, but received chronic acoustic stimulation. Auditory brainstem response thresholds were followed over time at 1, 2, 6, and 16 kHz. At the end of the study, the following cochlear measures were quantified: hair cells, spiral ganglion neuron density, fibrous tissue density, and stria vascularis blood vessel density; the presence or absence of ossification around the electrode entry was also noted. After surgery, implanted animals experienced a range of 0-55 dB of threshold shifts in the vicinity of the electrode at 6 and 16 kHz. The degree of hearing loss was significantly correlated with reduced stria vascularis vessel density and with the presence of ossification, but not with hair cell counts, spiral ganglion neuron density, or fibrosis area. After 10 weeks of stimulation, 67% of implanted, stimulated animals had more than 10 dB of additional threshold shift at 1 kHz, compared to 17% of implanted, non-stimulated animals and 0% of non-implanted animals. This 1-kHz hearing loss was not associated with changes in any of the cochlear measures quantified in this study. The variation in hearing loss after surgery and electrical stimulation in this animal model is consistent with the variation in human patients. Further, these findings illustrate an advantage of a normal-hearing animal model for quantification of hearing loss and damage to cochlear structures without the confounding effects

of chemical- or noise-induced hearing loss. Finally, this study is the first to suggest a role of the stria vascularis and damage to the lateral wall in implantation-induced hearing loss. Further work is needed to determine the mechanisms of implantation- and electrical-stimulation-induced hearing loss.

Thom, K. A., Standiford, H. C., Kristie Johnson, J., Hanna, N., & Furuno, J. P. (2014). Effectiveness of an antimicrobial polymer to decrease contamination of environmental surfaces in the clinical setting. *Infection Control and Hospital Epidemiology, 35*(8), 1060-1062.

We performed a real-world, controlled intervention to investigate use of an antimicrobial surface polymer, MSDS Poly, on environmental contamination. Pathogenic bacteria were identified in 18 (90%) of 20 observations in treated rooms and 19 (83%) of 23 observations in untreated rooms (P =.67). MSDS Poly had no significant effect on environmental contamination.

Thorn, S. R., Baquero, K. C., Newsom, S. A., El Kasmi, K. C., Bergman, B. C., Shulman, G. I., et al. (2014). Early life exposure to maternal insulin resistance has persistent effects on hepatic NAFLD in juvenile nonhuman primates. *Diabetes, 63*(8), 2702-2713.

The origins of nonalcoholic fatty liver disease (NAFLD) may lie in early intrauterine exposures. Here we examined the maternal response to chronic maternal high-fat (HF) diet and the impact of postweaning healthy diet on mechanisms for NAFLD development in juvenile nonhuman primate (NHP) offspring at 1 year of age. Pregnant females on HF diet were segregated as insulin resistant (IR; HF+IR) or insulin sensitive (IS; HF+IS) compared with control (CON)-fed mothers. HF+IR mothers have increased body mass, higher triglycerides, and increased placental cytokines. At weaning, offspring were placed on a CON or HF diet. Only offspring from HF+IR mothers had increased liver triglycerides and upregulated pathways for hepatic de novo lipid synthesis and inflammation that was irreversible upon switching to a healthy diet. These juvenile livers also showed a combination of classical and alternatively activated hepatic macrophages and natural killer T cells, in the absence of obesity or insulin resistance. Our findings suggest that maternal insulin resistance, including elevated triglycerides, insulin, and weight gain, initiates dysregulation of the juvenile hepatic immune system and development of de novo lipogenic

pathways that persist in vitro and may be an irreversible "first hit" in the pathogenesis of NAFLD in NHP. © 2014 by the American Diabetes Association.

Tilki, D., Hu, B., Nguyen, H. G., Dall'Era, M. A., Bertini, R., Carballido, J. A., et al. (2014). Impact of synchronous metastasis distribution on cancer-specific survival in renal cell carcinoma after radical nephrectomy with tumor thrombectomy. *The Journal of Urology,*

PURPOSE: Metastatic renal cell carcinoma (RCC) can be clinically diverse in terms of the pattern of metastatic disease and response to treatment. We studied the impact of metastasis and location on cancer-specific survival (CSS). PATIENTS AND METHODS: The records of 2017 patients with RCC and tumor thrombus who underwent radical nephrectomy and tumor thrombectomy from 1971 to 2012 at 22 centers in the United States and Europe were analyzed. Number and location of synchronous metastases were compared with respect to patients' CSS. Multivariable Cox regression models were used to quantify the impact of covariates. RESULTS: Lymph node (n=155) or distant metastasis (n=725) were present in 880 (44%) of the patients. In patients with distant disease, 385 (53%) had an isolated metastasis. 5-year-CSS was 51.3% (CI 48.6%-53.9%) in the entire group. In univariable analysis, patients with isolated lymph node metastasis had a significantly worse CSS compared with patients with a solitary distant metastasis. The location of distant metastasis did not have any significant effect on CSS. In multivariable analysis, the presence of lymph node metastasis, isolated distant metastasis, and multiple distant metastases were independently associated with CSS. Moreover, higher tumor thrombus level, papillary histology, and the use of postoperative systemic therapy were independently associated with worse CSS. CONCLUSIONS: In our multi-institutional series of patients with RCC who underwent radical nephrectomy and tumor thrombectomy, almost half of the patients had synchronous lymph node or distant organ metastasis. Survival was superior in patients with solitary distant metastasis compared with isolated lymph node disease.

Tisherman, S. A., Schmicker, R. H., Brasel, K. J., Bulger, E. M., Kerby, J. D., Minei, J. P., et al. (2014). Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the resuscitation outcomes consortium. *Annals of Surgery,*

OBJECTIVE:: To identify causes and timing of mortality in trauma patients to determine targets

for future studies. BACKGROUND:: In trials conducted by the Resuscitation Outcomes Consortium in patients with traumatic hypovolemic shock (shock) or traumatic brain injury (TBI), hypertonic saline failed to improve survival. Selecting appropriate candidates is challenging. METHODS:: Retrospective review of patients enrolled in multicenter, randomized trials performed from 2006 to 2009. Inclusion criteria were as follows: injured patients, age 15 years or more with hypovolemic shock [systolic blood pressure (SBP) /= 108) or severe TBI [Glasgow Coma Score (GCS) </= 8]. Initial fluid administered was 250 mL of either 7.5% saline with 6% dextran 70, 7.5% saline or 0.9% saline. RESULTS:: A total of 2061 subjects were enrolled (809 shock, 1252 TBI) and 571 (27.7%) died. Survivors were younger than nonsurvivors [30 (interquartile range 23) vs 42 (34)] and had a higher GCS, though similar hemodynamics. Most deaths occurred despite ongoing resuscitation. Forty-six percent of deaths in the TBI cohort were within 24 hours, compared with 82% in the shock cohort and 72% in the cohort with both shock and TBI. Median time to death was 29 hours in the TBI cohort, 2 hours in the shock cohort, and 4 hours in patients with both. Sepsis and multiple organ dysfunction accounted for 2% of deaths. CONCLUSIONS:: Most deaths from trauma with shock or TBI occur within 24 hours from hypovolemic shock or TBI. Novel resuscitation strategies should focus on early deaths, though prevention may have a greater impact.

Tjaden, K., Kain, A., & Lam, J. (2014). Hybridizing conversational and clear speech to investigate the source of increased intelligibility in speakers with parkinson's disease. *Journal of Speech, Language, and Hearing Research, 57*(4), 1191-1205.

Purpose: A speech analysis-resynthesis paradigm was used to investigate segmental and suprasegmental acoustic variables explaining intelligibility variation for 2 speakers with Parkinson's disease (PD). Method: Sentences were read in conversational and clear styles. Acoustic characteristics from clear sentences were extracted and applied to conversational sentences, yielding 6 hybridized versions of sentences in which segment durations, short-term spectrum, energy characteristics, or fundamental frequency characteristics for clear productions were applied individually or in combination to conversational productions. Listeners (N = 20) judged intelligibility in transcription and scaling tasks. Results: Intelligibility increases above conversation were more robust for transcription, but the pattern of intelligibility improvement

was similar across tasks. For 1 speaker, hybridization involving only clear energy characteristics yielded an 8.7% improvement in transcription intelligibility above conversation. For the other speaker, hybridization involving clear spectrum yielded an 18% intelligibility improvement, whereas hybridization involving both clear spectrum and duration yielded a 13.4% improvement. Conclusions: Not all production changes accompanying clear speech explain its improved intelligibility. Suprasegmental adjustments contributed to intelligibility improvements when segmental adjustments, as inferred from vowel space area, were not robust. Hybridization can be used to identify acoustic variables explaining intelligibility variation in mild dysarthria secondary to PD. © American Speech-Language-Hearing Association.

Tommaso, C. L., Fullerton, D. A., Feldman, T., Dean, L. S., Hijazi, Z. M., Horlick, E., et al. (2014). SCAI/AATS/ACC/STS operator and institutional requirements for transcatheter valve repair and replacement. part II. mitral valve. *Journal of Thoracic and Cardiovascular Surgery, 148*(2), 387-400.

Tratnyek, P. G., Salter, A. J., Nurmi, J. T., & Sarathy, V. (2010). *Environmental applications of zerovalent metals: Iron vs. zinc* American Chemical Society.

The reactivity of particulate zero-valent metals in solution is affected by the metal type (e.g., Fe vs. Zn), particle size (nano vs. micro), surface conditions (passivation by coatings of oxides), and solution conditions (including the type and concentration of oxidants). Comparing the reactivity of various types of Fe0 and Zn0 with carbon tetrachloride (CCl4) shows that the intended effect of properties engineered to give enhanced reactivity can be obscured by effects of environmental factors. In this case, rates of CCl4 reduction by Zn0 are more strongly affected by solution chemistry than particle size or surface morphology. Under favorable conditions, however, Zn0 reduces CCl 4 more rapidly-and more completely-than Fe0, regardless of particle size. The suitability of nano-sized Zn0 for environmental remediation applications is uncertain. © 2010 American Chemical Society.

Troxell, M. L., Higgins, J. P., & Kambham, N. (2014). Renal pathology associated with hematopoietic stem cell transplantation. *Advances in Anatomic Pathology, 21*(5), 330-340.

The kidney is subject to a large variety of injurious factors before, during, and after

hematopoietic stem cell transplantation (HCT), leading to a high incidence of acute kidney injury in the peritransplant period. Chronic kidney disease is estimated to impact 15% to 20% of HCT recipients. Although renal biopsies may be deferred in the setting of thrombotic microangiopathy, acute self-limited impairment, or slowly progressive functional decline, in many patients renal biopsy yields important diagnostic insight to guide treatment. Light microscopic, immunofluorescence, and ultrastructural analysis often reveals a number of concurrent abnormalities in glomeruli, tubules, interstitium, and vessels. Meta-analysis of the literature reveals that membranous nephropathy is the most commonly reported glomerular lesion in the setting of HCT, followed by minimal change disease. Autopsy and biopsy studies show that clinical criteria lack sensitivity and specificity for renal acute and chronic thrombotic microangiopathy. Viral infection and other causes of interstitial nephritis and tubular injury are important findings in HCT renal biopsies, which in many instances may not be clinically suspected. Given the complexity and variability of HCT protocols, clinicopathologic correlation is needed.

Tseng, J., Dhungel, B., Mills, J. K., Diggs, B. S., Weerasinghe, R., Fortino, J., et al. (2014). Merkel cell carcinoma: What makes a difference? *American Journal of Surgery,*

BACKGROUND: Merkel cell carcinoma (MCC) is a cutaneous neuroendocrine tumor that may spread via lymphatics and can therefore be staged with sentinel lymph node biopsy (SLNB). MCC is radiosensitive and chemosensitive, although the role of adjuvant therapy is still unclear. We examined the impact of different treatments on the outcome of MCC. METHODS: We performed a retrospective review of state cancer registry data from California, Oregon, and Washington of patients diagnosed with primary skin MCC between 1988 and 2012 (n = 4,038). Data were analyzed using Cox regression and Kaplan-Meier methods to examine disease-specific survival. RESULTS: Patients with positive nodes or no documented nodal evaluation had worse survival compared with node-negative patients. No nodal evaluation had decreased survival compared with lymph node evaluation by SLNB. Completion lymph node dissection conferred improved survival in patients with a positive SLNB. In clinically node-negative patients who had a positive SLNB, radiation and chemotherapy did not affect survival. CONCLUSIONS: Lymph node evaluation is an important component to MCC treatment. The role of adjuvant radiation and chemotherapy needs further evaluation.

Uhrenholt, L., Webb, A., & Freeman, M. (2014). Letter to the editor regarding "do X-ray-occult fractures play a role in chronic pain following a whiplash injury?" by hertzum-larsen R, petersen H, kasch H, bendix T. eur spine J. 2014; DOI 10.1007/s00586-014-3362-3. *European Spine Journal,*

Van Nostrand, J. L., Brady, C. A., Jung, H., Fuentes, D. R., Kozak, M. M., Johnson, T. M., et al. (2014). Inappropriate p53 activation during development induces features of CHARGE syndrome. *Nature,* CHARGE syndrome is a multiple anomaly disorder in which patients present with a variety of phenotypes, including ocular coloboma, heart defects, choanal atresia, retarded growth and development, genitourinary hypoplasia and ear abnormalities. Despite 70-90% of CHARGE syndrome cases resulting from mutations in the gene CHD7, which encodes an ATP-dependent chromatin remodeller, the pathways underlying the diverse phenotypes remain poorly understood. Surprisingly, our studies of a knock-in mutant mouse strain that expresses a stabilized and transcriptionally dead variant of the tumour-suppressor protein p53 (p5325,26,53,54), along with a wild-type allele of p53 (also known as Trp53), revealed late-gestational embryonic lethality associated with a host of phenotypes that are characteristic of CHARGE syndrome, including coloboma, inner and outer ear malformations, heart outflow tract defects and craniofacial defects. We found that the p5325,26,53,54 mutant protein stabilized and hyperactivated wild-type p53, which then inappropriately induced its target genes and triggered cell-cycle arrest or apoptosis during development. Importantly, these phenotypes were only observed with a wild-type p53 allele, as p5325,26,53,54/- embryos were fully viable. Furthermore, we found that CHD7 can bind to the p53 promoter, thereby negatively regulating p53 expression, and that CHD7 loss in mouse neural crest cells or samples from patients with CHARGE syndrome results in p53 activation. Strikingly, we found that p53 heterozygosity partially rescued the phenotypes in Chd7-null mouse embryos, demonstrating that p53 contributes to the phenotypes that result from CHD7 loss. Thus, inappropriate p53 activation during development can promote CHARGE phenotypes, supporting the idea that p53 has a critical role in developmental syndromes and providing important insight into the mechanisms underlying CHARGE syndrome.

Viecelli, H. M., Harbottle, R. P., Wong, S. P., Schlegel, A., Chuah, M. K., Vandendriessche, T., et al. (2014). *Treatment of phenylketonuria using minicircle-based naked-DNA gene transfer to murine liver*

Host immune response to viral vectors, persistence of nonintegrating vectors, and sustained transgene expression are among the major challenges in gene therapy. To overcome these hurdles, we successfully used minicircle (MC) naked-DNA vectors devoid of any viral or bacterial sequences for the long-term treatment of murine phenylketonuria, a model for a genetic liver defect. MC-DNA vectors expressed the murine phenylalanine hydroxylase (Pah) complementary DNA (cDNA) from a liver-specific promoter coupled to a de novo designed hepatocyte-specific regulatory element, designated P3, which is a cluster of evolutionary conserved transcription factor binding sites. MC-DNA vectors were subsequently delivered to the liver by a single hydrodynamic tail vein (HTV) injection. The MC-DNA vector normalized blood phenylalanine concomitant with reversion of hypopigmentation in a dose-dependent manner for more than 1 year, whereas the corresponding parental plasmid did not result in any phenylalanine clearance. MC vectors persisted in an episomal state in the liver consistent with sustained transgene expression and hepatic PAH enzyme activity without any apparent adverse effects. Moreover, 14-20% of all hepatocytes expressed transgenic PAH, and the expression was observed exclusively in the liver and predominately around pericentral areas of the hepatic lobule, while there was no transgene expression in periportal areas. Conclusion: This study demonstrates that MC technology offers an improved safety profile and has the potential for the genetic treatment of liver diseases. © 2014 by the American Association for the Study of Liver Diseases.

Wacholder, A. C., Cox, C., Meyer, T. J., Ruggiero, R. P., Vemulapalli, V., Damert, A., et al. (2014). Inference of transposable element ancestry. *PLoS Genetics, 10*(8), e1004482.

Most common methods for inferring transposable element (TE) evolutionary relationships are based on dividing TEs into subfamilies using shared diagnostic nucleotides. Although originally justified based on the "master gene" model of TE evolution, computational and experimental work indicates that many of the subfamilies generated by these methods contain multiple source elements. This implies that subfamily-based methods give an incomplete picture of TE relationships. Studies on selection, functional exaptation, and predictions of horizontal transfer

may all be affected. Here, we develop a Bayesian method for inferring TE ancestry that gives the probability that each sequence was replicative, its frequency of replication, and the probability that each extant TE sequence came from each possible ancestral sequence. Applying our method to 986 members of the newly-discovered LAVA family of TEs, we show that there were far more source elements in the history of LAVA expansion than subfamilies identified using the CoSeg subfamily-classification program. We also identify multiple replicative elements in the AluSc subfamily in humans. Our results strongly indicate that a reassessment of subfamily structures is necessary to obtain accurate estimates of mutation processes, phylogenetic relationships and historical times of activity.

Wang, J., Zhang, V. W., Feng, Y., Tian, X., Li, F. Y., Truong, C., et al. (2014). Dependable and efficient clinical utility of target capture based deep sequencing in molecular diagnosis of retinitis pigmentosa. *Investigative Ophthalmology & Visual Science,*

PURPOSE: The purpose of this study is to establish a fully validated, high throughput next generation sequencing (NGS) approach for comprehensive, cost-effective, clinical molecular diagnosis of retinitis pigmentosa (RP). METHODS: Target sequences of a panel of 66 genes known to cause all nonsyndromic and a few syndromic forms of RP were enriched by using custom designed probe hybridization. A total of 939 coding exons and 20 bp of their flanking intron regions with a total of 202,800 bp of target sequences were captured, followed by massively parallel sequencing (MPS) on the Illumina HiSeq2000 device. RESULTS: Twelve samples with known mutations were used for test validation. We achieved an average sequence depth of ~1000X per base. Exons with <20X insufficient coverage were completed by PCR/Sanger sequencing to ensure 100% coverage. We analyzed DNA from 65 unrelated RP patients, and detected deleterious mutations in 53 patients with a diagnostic yield of ~82%. CONCLUSIONS: Clinically validated, and consistently deep coverage of individual exons allows the accurate identification of all types of mutations including point mutations, exonic deletions and large insertions. Our comprehensive MPS approach greatly improves diagnostic acumen for RP in a cost- and time-efficient manner.

Whellan, D. J., Goldstein, J. L., Cryer, B. L., Eisen, G. M., Lanas, A., Miller, A. B., et al. (2014). PA32540 (a coordinated-delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) versus enteric-coated aspirin 325 mg alone in subjects at risk for aspirin-associated gastric ulcers: Results of two 6-month, phase 3 studies. *American Heart Journal,* Discontinuations and/or interruptions in aspirin therapy for secondary cardioprotection due to upper gastrointestinal (UGI) complications or symptoms have been shown to increase the risk for subsequent cardiovascular events. PA32540 is a coordinated-delivery, combination tablet consisting of enteric-coated aspirin (EC-ASA) 325 mg and immediate-release (IR) omeprazole 40 mg. Methods: Two identically-designed, 6-month, randomized, double-blind trials evaluated PA32540 vs. EC-ASA 325 mg in a secondary cardiovascular disease prevention population taking aspirin 325 mg daily for ≥3 months and at risk for ASA-associated gastric ulcers (GUs). The combined study population was 1049 subjects (524 randomized to PA32540, 525 to EC-ASA 325 mg). The primary endpoint was the occurrence of endoscopically-determined gastric ulceration over 6 months. Safety outcomes included the rates of major adverse cardiovascular events (MACE) and UGI symptoms. Results: Significantly fewer PA32540-treated subjects (3.2%) developed endoscopic GUs vs. EC-ASA 325 mg-treated subjects (8.6%) (P < .001). Overall occurrence of MACE was low (2.1%), with no significant differences between treatments in types or incidence of MACE. PA32540-treated subjects had significantly fewer UGI symptoms (P < .001) and significantly fewer discontinuations due to pre-specified UGI adverse events (1.5% vs. 8.2%, respectively; P < .001). Conclusions: PA32540 reduced the incidence of endoscopic GUs compared to EC-ASA 325 mg, but with a similar cardiovascular event profile. Due to fewer UGI symptoms, continuation on aspirin therapy was greater in the PA32540 treatment arm. © 2014 Mosby, Inc.

Wiener, R. S., & Slatore, C. G. (2014). Real-world evidence about potential psychosocial harms of lung cancer screening. *JAMA Internal Medicine, 174*(8), 1416.

Williams, C. L., Buchta, W. C., & Riegel, A. C. (2014). CRF-R2 and the heterosynaptic regulation of VTA glutamate during reinstatement of cocaine seeking. *Journal of Neuroscience, 34*(31), 10402-10414.

Stress can reinstate cocaine seeking through an interaction between the stress hormone corticotropin releasing factor (CRF) and glutamate release onto dopamine neurons in the ventral tegmental area (VTA). To better understand the underlying causes, synaptic mechanisms were investigated in brain slices from rats. In control tissue, EPSCs displayed concentration-dependent, bimodal responses to CRF potentiation atlow concentrations (3-100 nM) and attenuation athigher concentrations (300 nM). EPSC potentiation and attenuation were mediated by CRF-R1 and CRF-R2 receptor subtypes, respectively, localized to presynaptic terminals. The CRF-R2 attenuation was blocked by the GABA-B receptor antagonist CGP55843. Additional recordings of GABA-A IPSCs showed CRF-R2 activation-facilitated presynaptic release of GABA, suggesting that CRF-R2 may regulate glutamate release via heterosynaptic facilitation of GABA synapses. After chronic cocaine self-administration and extinction training, the sensitivity of glutamate and GABA receptors was unchanged. However, the ability of CRF-R2 agonists to depress EPSCs and potentiate IPSCs was diminished. After yohimbine plus cue reinstatement, the actions of CRF-R2 on GABA and glutamate release were reversed. CRF-R2 activation increased EPSCs as a resultofa reduction oftonic GABA-dependent inhibition. After reinstatement, application of the A1 adenosine antagonist 1,3-dipropyl-8-cyclopentylxanthine increased GABA tone to inhibit the CRF-R2 action. Blockade of GABA-B receptors prevented both the CRF-R2 increase in EPSCs and the attenuation produced by 1,3-dipropyl-8-cyclopentylxanthine. These studies demonstrate that presynaptic CRF-R1/R2 tightly regulate glutamate transmission in the VTA via a concerted, heterosynaptic manner that may become altered by stress-related pathologies, such as addiction.

Willson, D. F., Kirby, A., & Kicker, J. S. (2014). Respiratory secretion analyses in the evaluation of ventilator-associated pneumonia: A survey of current practice in pediatric critical care. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies,*

OBJECTIVE:: Ventilator-associated pneumonia is among the most common nosocomial infections in the PICU. Respiratory secretion cultures and Gram stains are frequently obtained for diagnosis and to guide therapy, but their specificity is questionable. We conducted a scenario-based survey of pediatric intensivists to assess their antibiotic use in response to hypothetical tracheal aspirate

culture and Gram stain results. DESIGN:: Scenario-based survey. SETTING:: A hypothetical PICU. PATIENTS:: Three hypothetical scenarios of intubated children with fever and leukocytosis: a 4-month-old child with respiratory syncytial virus infection; a 7-year-old child with acute respiratory distress syndrome; and a 10-year-old child with aspiration pneumonia. INTERVENTIONS:: Scenario-based survey of pediatric intensivists from the Pediatric Acute Lung Injury and Sepsis Network. MEASUREMENTS AND MAIN RESULTS:: Ninety-four percent of the pediatric intensivists surveyed would obtain a respiratory secretion culture and Gram stain in the evaluation of an intubated child with fever and leukocytosis, most by simple tracheal aspiration but a minority (32%) by bronchoalveolar lavage. "Bacterial pathogenicity" was considered the most important result of the analysis. Although there were some differences across the three scenarios, most would initiate antibiotics if culture results identified methicillin-sensitive or methicillin-resistant Staphylococcus aureus or Pseudomonas and, on average, continue antibiotics for 7-10 days. CONCLUSIONS:: The majority of pediatric intensivists would obtain respiratory secretion cultures and Gram stains in the evaluation of an intubated child with fever and leukocytosis and initiate antibiotics guided by the results. The specificity of respiratory secretion cultures and Gram stains for the diagnosis of ventilator-associated pneumonia requires critical evaluation as this diagnosis is responsible for more than half of antibiotic use in the PICU.

Wilson, A. C. (2014). Trajectories of pain and functional disability in CBT for pediatric chronic pain: Is statistically significant change meaningful to patients and families? *Pain,*

Witkop, M., Cutter, S., Deutsche, J., Santaella, M., Chapman, R., Lafranco, J., et al. (2014). Emerging therapies for hemophilia: A new era of care and the role of the interdisciplinary team. *Seminars in Thrombosis and Hemostasis,*

The introduction of new hemophilia management therapies, targeting extended half-lives through bioengineering, ushers in an era of potential promise and increasing complexity, more so for those with hemophilia B than hemophilia A. Questions arise for patients, caregivers, and hemophilia treatment center (HTC) staff about how to assess and incorporate novel therapies and how to determine whether new therapies offer a distinct advantage over established treatment routines. Nurses and other interdisciplinary HTC staff are well positioned to assess, educate, and

support patients and families in navigating this rapidly changing landscape. To support these challenging efforts, this review offers a perspective on issues affecting therapeutic transitions and provides tools to foster ongoing adherence.

Woods, T. R., Cohen, D. M., Islam, M. N., Kratochvil, F. J., Stewart, J. C. B., Reeder, S. L., et al. (2014). Intraoral basal cell carcinoma, a rare neoplasm: Report of three new cases with literature review. *Head and Neck Pathology, 8*(3), 339-348.

Intraoral basal cell carcinoma (IOBCC) is an extremely rare entity that bears close microscopic resemblance to and is often confused with the peripheral ameloblastoma (PA). Basal cell carcinomas are thought to arise from pluripotential basal cells present within surface epithelium and adnexal structures, so theoretically they can arise within the oral cavity. Many of the early cases reported as IOBCC actually represent PA. Most of the well documented cases arise from the gingiva. The histologic features of basal cell carcinoma that help separate it from a PA include: tumor arising from surface epithelium, scattered mitotic figures and apoptotic cells, presence of mucoid ground substance and tumor infiltrating widely throughout the connective tissue and often exhibiting a prominent retraction artifact. Clinically IOBCC resemble carcinomas, compared to the benign and innocuous appearance of the PA and typically presents as surface ulcerations varying from rodent ulcer to an ulcerated erythroplakia appearance. This contrasts with the classic "bump on the gum" appearance of PAs with usually intact surface and appearing as small discrete, sessile, exophytic lesions. Importantly, the proliferative basaloid epithelium demonstrates positive immunoreactivity for the anti-epithelial antibody, Ber-EP4, a cell surface glycoprotein. The IOBCC has the potential for local recurrence and aggressive behavior and should be treated with wide surgical excision and close clinical follow up. We present 3 rare cases of IOBCC and discuss the salient histologic, immunohistochemical and clinical features. © 2013 Springer Science+Business Media New York.

Xie, L., Liang, T., Kang, Y., Lin, X., Sobbi, R., Xie, H., et al. (2014). Phosphatidylinositol 4,5-biphosphate (PIP) modulates syntaxin-1A binding to sulfonylurea receptor 2A to regulate cardiac ATP-sensitive potassium (K) channels. *Journal of Molecular and Cellular Cardiology, 75C*, 100-110.

Cardiac sarcolemmal syntaxin (Syn)-1A interacts with sulfonylurea receptor (SUR) 2A to inhibit ATP-sensitive potassium (KATP) channels. Phosphatidylinositol 4,5-bisphosphate (PIP2), a ubiquitous endogenous inositol phospholipid, known to bind Kir6.2 subunit to open KATP channels, has recently been shown to directly bind Syn-1A in plasma membrane to form Syn-1A clusters. Here, we sought to determine whether the interaction between Syn-1A and PIP2 interferes with the ability of Syn-1A to bind SUR2A and inhibit KATP channel activity. We found that PIP2 dose-dependently reduced SUR2A binding to GST-Syn-1A by in vitro pulldown assays. FRET studies in intact cells using TIRFM revealed that increasing endogenous PIP2 levels led to increased Syn-1A (-EGFP) cluster formation and a severe reduction in availability of Syn-1A molecules to interact with SUR2A (-mCherry) molecules outside the Syn-1A clusters. Correspondingly, electrophysiological studies employing SUR2A/Kir6.2-expressing HEK cells showed that increasing endogenous or exogenous PIP2 diminished the inhibitory effect of Syn-1A on KATP currents. The physiological relevance of these findings was confirmed by ability of exogenous PIP2 to block exogenous Syn-1A inhibition of cardiac KATP currents in inside-out patches of mouse ventricular myocytes. The effect of PIP2 on physical and functional interactions between Syn-1A and KATP channels is specific and not observed with physiologic concentrations of other phospholipids. To unequivocally demonstrate the specificity of PIP2 interaction with Syn-1A and its impact on KATP channel modulation by Syn-1A, we employed a PIP2-insensitive Syn-1A-5RK/A mutant. The Syn-1A-5RK/A mutant retains the ability to interact with SUR2A in both in vitro binding and in vivo FRET assays, although as expected the interaction is no longer disrupted by PIP2. Interestingly, at physiological PIP2 concentrations, Syn-1A-5RK/A inhibited KATP currents to a greater extent than Syn-1A-WT, indicating that the inhibitory effect of Syn-1A on KATP channels is not due to direct competition between Syn-1A and Kir6.2 for PIP2 binding. At high-dose PIP2, however, inhibition of KATP currents by Syn-1A-5RK/A was greatly reduced, likely overridden by the direct activating effect of PIP2 on KATP channels. Finally, depleting endogenous PIP2 with polyphosphoinositide phosphatase synaptojanin-1 known to disperse Syn-1A clusters, freed Syn-1A from Syn-1A clusters to bind SUR2A, causing optimal inhibition of KATP channels. These results taken together led us to conclude that PIP2 affects cardiac KATP channels not only by its actions on the channel directly but also by multi-modal effects of dynamically

modulating Syn-1A mobility from Syn-1A clusters and thereby the availability of Syn-1A to inhibit KATP channels via interaction with SUR2A on the plasma membrane.

Yang, R., Kong, E., Jin, J., Hergovich, A., & Püschel, A. W. (2014). Rassf5 and ndr kinases regulate neuronal polarity through Par3 phosphorylation in a novel pathway. *Journal of Cell Science, 127*(16), 3463-3476.

The morphology and polarized growth of cells depend on pathways that control the asymmetric distribution of regulatory factors. The evolutionarily conserved Ndr kinases play important roles in cell polarity and morphogenesis in yeast and invertebrates but it is unclear whether they perform a similar function in mammalian cells. Here, we analyze the function of mammalian Ndr1 and Ndr2 (also known as STK38 or STK38L, respectively) in the establishment of polarity in neurons. We show that they act downstream of the tumor suppressor Rassf5 and upstream of the polarity protein Par3 (also known as PARD3). Rassf5 and Ndr1 or Ndr2 are required during the polarization of hippocampal neurons to prevent the formation of supernumerary axons. Mechanistically, the Ndr kinases act by phosphorylating Par3 at Ser383 to inhibit its interaction with dynein, thereby polarizing the distribution of Par3 and reinforcing axon specification. Our results identify a novel Rassf5-Ndr-Par3 signaling cascade that regulates the transport of Par3 during the establishment of neuronal polarity. Their role in neuronal polarity suggests that Ndr kinases perform a conserved function as regulators of cell polarity. © 2014. Published by The Company of Biologists Ltd.

Yaylali, I., Ju, H., Yoo, J., Ching, A., & Hart, R. (2014). Intraoperative neurophysiological monitoring in anterior lumbar interbody fusion surgery. *Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society, 31*(4), 352-355.

PURPOSE: Somatosensory evoked potential (SSEP) and motor evoked potentials (MEP) are frequently fused to monitor neurological function during spinal deformity surgery. However, there are few studies regarding the utilization of intraoperative neuromonitoring during anterior lumbar interbody fusion (ALIF). This study presents the authors' experience with intraoperative neuromonitoring in ALIF. METHODS: A retrospective review of all patients undergoing ALIF with intraoperative neuromonitoring from November 2008 to July 2013 was performed. Factors

including gender, operative time, blood loss, and number and levels of interbody fusions were analyzed as risk factors for interoperational alerts. RESULTS: A total of 189 consecutive patients who underwent ALIFs were studied. All 189 patients had SSEP, and 131 patients had MEP as part of the intraoperative neuromonitoring in addition. The remaining 58 patients did not have MEP due to neuromuscular blockade requested by the exposure surgeon. There were no isolated intraoperative MEP changes. A total of 15 (7.9%) patients experienced intraoperative alerts. Thirteen (6.8%) of them were in SSEP. Two (1.1%) had MEP and SSEP changes together. None of these patients had new neurologic deficits postoperatively because of the surgeon's responses to the intraoperative alert. Increased risk of SSEP changes was seen in patients undergoing fusion of both L4/5 and L5/S1 ($P = 0.024$) and longer surgical duration ($P = 0.036$). No correlation was found between age and positive SSEP changes ($P > 0.05$). CONCLUSIONS: Somatosensory evoked potential changes occur relatively, frequently, and intraoperatively during ALIF. No patients with positive intraoperative SSEP changes demonstrated new postoperational deficits. Concurrent fusion of both the L4/5 and L5/S1 levels was significant risk factors for SSEP changes leading to intraoperative alerts. Operative duration and increased blood loss during surgery trended toward but did not reach statistical significance.

Yedinak, C. G., & Fleseriu, M. (2014). Self-perception of cognitive function among patients with active acromegaly, controlled acromegaly, and non-functional pituitary adenoma: A pilot study. *Endocrine, 46*(3), 585-593.

Pituitary adenomas (PAs) represent 15 % of all brain tumors. One-sixth of these are reported to cause acromegaly via excess growth hormone secretion. These tumors have been associated with multiple comorbidities, including neuropsychiatric and cognitive dysfunction. We aimed to assess patient perception of cognitive deficits and the relationship of cognitive changes to active acromegaly (AA) versus controlled acromegaly (CA) versus non-functional PAs (NFPA). A modified FACT-Cog survey was used, which focused on the prevalence and severity of perceived dysfunction in five areas of cognitive function: ability to learn, concentration/distractibility, mental agility, memory and recall, and verbal recall. Patient perception of current health and health change over the previous 12 months was also assessed. The overall perceived prevalence and severity of cognitive dysfunction were the highest among NFPA groups, particularly in the

areas of mental agility, verbal recall, and memory/recall. Patients with AA reported greater prevalence and severity of dysfunction with respect to concentration/distractibility and ability to learn. Patients with AA reported the best overall current health, though patients with CA reported the greatest improvement in health over the previous year. These findings may indicate that PAs can affect cognitive function regardless of whether excess growth hormone is present. Acromegaly and NFPA patients perceive specific areas of cognitive dysfunction that may require further evaluation and treatment. Further research may be useful regarding patient quality of life, patient functionality during normal daily activities, and perceived dysfunction despite biological disease control. © 2013 Springer Science+Business Media.

Yedinak, C. G., McCartney, S., Dillard, T. H., Wei, K. S., & Fleseriu, M. (2014). Case report: Reversible cabergoline-associated cardiac valvulopathy post drug discontinuation. *F1000research, 3*, 171.
We present a case of a 21 year old male patient diagnosed with a 2.2 cm prolactin-secreting adenoma in contact with the optic chiasm. The patient was treated with up to 6mg/week of cabergoline (total cumulative dose 814 mg) and developed mild valvulopathy. Valvulopathy was subsequently reversed after discontinuation of cabergoline therapy.

Yoo, J. U. (2014). Commentary: Dysphagia after anterior cervical spine surgery. *The Spine Journal : Official Journal of the North American Spine Society, 14*(9), 2261-2262.
COMMENTARY ON: Joaquim AF, Murar J, Savage JW, Patel AA. Dysphagia after anterior cervical spine surgery: a systematic review of potential preventative measures. Spine J 2014;14;2246-60 (in this issue).

Zabriskie, M. S., Eide, C. A., Tantravahi, S. K., Vellore, N. A., Estrada, J., Nicolini, F. E., et al. (2014). BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in ph chromosome-positive leukemia. *Cancer Cell,*
Ponatinib is the only currently approved tyrosine kinase inhibitor (TKI) that suppresses all BCR-ABL1 single mutants in Philadelphia chromosome-positive (Ph+) leukemia, including the recalcitrant BCR-ABL1T315I mutant. However, emergence of compound mutations in a BCR-ABL1 allele may confer ponatinib resistance. We found that clinically reported BCR-ABL1 compound mutants center on 12 key positions and confer varying resistance to imatinib, nilotinib, dasatinib,

ponatinib, rebastinib, and bosutinib. T315I-inclusive compound mutants confer high-level resistance to TKIs, including ponatinib. In vitro resistance profiling was predictive of treatment outcomes in Ph+ leukemia patients. Structural explanations for compound mutation-based resistance were obtained through molecular dynamics simulations. Our findings demonstrate that BCR-ABL1 compound mutants confer different levels of TKI resistance, necessitating rational treatment selection to optimize clinical outcome.

Zerbe, K. J. (2002). Giving birth to new dreams. *Bulletin of the Menninger Clinic, 66*(4), 369-377.

Zuckerman, K. E., Mattox, K. M., Sinche, B. K., Blaschke, G. S., & Bethell, C. (2014). Racial, ethnic, and language disparities in early childhood developmental/behavioral evaluations: A narrative review. *Clinical Pediatrics, 53*(7), 619-631.