References

Ahuja, C., Farsad, K., & Chadha, M. (2015). An overview of splenic embolization. *AJR.American Journal of Roentgenology, 205*(4), 720-725.

OBJECTIVE: The purpose of this article is to define the role of splenic embolization in trauma patients and in patients presenting for treatment of thrombocytopenia and portal hypertension. This article reviews the indications, technical considerations, outcomes, and complications of splenic artery embolization. CONCLUSION: Transcatheter splenic artery embolization has a major role in the management of traumatic splenic injuries and as an adjunctive procedure in the treatment of thrombocytopenia and portal hypertension.

Alt, J. A., DeConde, A. S., Mace, J. C., Steele, T. O., Orlandi, R. R., & Smith, T. L. (2015). Quality of life in patients with chronic rhinosinusitis and sleep dysfunction undergoing endoscopic sinus surgery: A pilot investigation of comorbid obstructive sleep apnea. *JAMA Otolaryngology-- Head & Neck Surgery,* , 1-9.

Importance: Patients with chronic rhinosinusitis (CRS) have reduced sleep quality linked to their overall well-being and disease-specific quality of life (QOL). Other primary sleep disorders also affect QOL. Objective: To determine the impact of comorbid obstructive sleep apnea (OSA) on CRS disease-specific QOL and sleep dysfunction in patients with CRS following functional endoscopic sinus surgery. Design, Setting, and Participants: Prospective multisite cohort study conducted between October 2011 and November 2014 at academic, tertiary referral centers with a population-based sample of 405 adults. Intervention: Functional endoscopic sinus surgery for medically refractory symptoms of CRS. Main Outcomes and Measures: Primary outcome measures consisted of preoperative and postoperative scores operationalized by the Rhinosinusitis Disability Index (RSDI) survey, the 22-item Sinonasal Outcome Test (SNOT-22), and the Pittsburgh Sleep Quality Index (PSQI). Obstructive sleep apnea was the primary, independent risk factor. Results: Of 405 participants, 60 (15%) had comorbid OSA. A total of 285 (70%) participants provided preoperative and postoperative survey responses, with a mean (SD) of 13.7 (5.3) months of follow-up. Significant postoperative improvement ($P < .05$) was reported across all mean disease-specific QOL measures for both participants with and without comorbid OSA. Participants without OSA reported significant greater improvement in unadjusted mean

(SD) RSDI global scores (-25.0 [23.3] vs -16.5 [22.1]; P = .03), RSDI physical (-10.7 [9.2] vs -7.3 [9.1]; P = .03) and functional (-8.4 [8.7] vs -5.1 [7.5]; P = .03) subdomain scores, and SNOT-22 rhinologic symptom domain scores (-9.1 [7.7] vs -5.7 [6.9]; P = .008). Participants without OSA also reported greater improvements on mean (SD) PSQI global (-1.9 [4.0] vs -0.5 [3.7]; P = .03), sleep quality (-0.4 [0.8] vs -0.03 [0.7]; P = .02), and sleep disturbance (-0.4 [0.7] vs -0.1 [0.7]; P = .03) scores. The majority of these associations were found to be durable after adjustment for alternate independent cofactors using stepwise linear regression modeling. Conclusions and Relevance: Patients with CRS and comorbid OSA have poor QOL with substantial disease-specific QOL improvements following surgery. Patients who present with CRS should be assessed for primary sleep disorders and, if identified, should be treated concurrently for both CRS and OSA to improve sleep dysfunction to optimize surgical outcomes. Trial Registration: clinicaltrials.gov Identifier: NCT01332136.

Alumkal, J. J., Slottke, R., Schwartzman, J., Cherala, G., Munar, M., Graff, J. N., et al. (2015). A phase II study of sulforaphane-rich broccoli sprout extracts in men with recurrent prostate cancer. *Investigational New Drugs, 33*(2), 480-489.

Alzhanov, D., Mukherjee, A., & Rotwein, P. (2015). Identifying growth hormone regulated enhancers in the Igf1 locus. *Physiological Genomics,* , physiolgenomics.00062.2015.
Growth hormone (GH) plays a central role in regulating somatic growth and in controlling multiple physiological processes in humans and other vertebrates. A key agent in many GH actions is the secreted peptide, IGF-I. As established previously, GH stimulates IGF-I gene expression via the Stat5b transcription factor, leading to production of IGF-I mRNAs and proteins. However, the precise mechanisms by which GH-activated Stat5b promotes IGF-I gene transcription have not been defined. Unlike other GH-regulated genes, there are no Stat5b sites near either of the two IGF-I gene promoters. Although dispersed GH-activated Stat5b binding elements have been mapped in rodent Igf1 gene chromatin, it is unknown how these distal sites might function as potential transcriptional enhancers. Here we have addressed mechanisms of regulation of IGF-I gene transcription by GH by generating cell lines in which the rat Igf1 chromosomal locus has been incorporated into the mouse genome. Using these cells we find that physiological levels of

GH rapidly and potently activate Igf1 gene transcription while stimulating physical interactions in chromatin between inducible Stat5b-binding elements and the Igf1 promoters. We have thus developed a robust experimental platform for elucidating how dispersed transcriptional enhancers control Igf1 gene expression under different biological conditions.

Amankwah, E. K., Lin, H. Y., Tyrer, J. P., Lawrenson, K., Dennis, J., Chornokur, G., et al. (2015). Epithelial-mesenchymal transition (EMT) gene variants and epithelial ovarian cancer (EOC) risk. *Genetic Epidemiology,*

Epithelial-mesenchymal transition (EMT) is a process whereby epithelial cells assume mesenchymal characteristics to facilitate cancer metastasis. However, EMT also contributes to the initiation and development of primary tumors. Prior studies that explored the hypothesis that EMT gene variants contribute to epithelial ovarian carcinoma (EOC) risk have been based on small sample sizes and none have sought replication in an independent population. We screened 15,816 single-nucleotide polymorphisms (SNPs) in 296 genes in a discovery phase using data from a genome-wide association study of EOC among women of European ancestry (1,947 cases and 2,009 controls) and identified 793 variants in 278 EMT-related genes that were nominally ($P < 0.05$) associated with invasive EOC. These SNPs were then genotyped in a larger study of 14,525 invasive-cancer patients and 23,447 controls. A P-value <0.05 and a false discovery rate (FDR) <0.2 were considered statistically significant. In the larger dataset, GPC6/GPC5 rs17702471 was associated with the endometrioid subtype among Caucasians (odds ratio (OR) = 1.16, 95% CI = 1.07-1.25, P = 0.0003, FDR = 0.19), whereas F8 rs7053448 (OR = 1.69, 95% CI = 1.27-2.24, P = 0.0003, FDR = 0.12), F8 rs7058826 (OR = 1.69, 95% CI = 1.27-2.24, P = 0.0003, FDR = 0.12), and CAPN13 rs1983383 (OR = 0.79, 95% CI = 0.69-0.90, P = 0.0005, FDR = 0.12) were associated with combined invasive EOC among Asians. In silico functional analyses revealed that GPC6/GPC5 rs17702471 coincided with DNA regulatory elements. These results suggest that EMT gene variants do not appear to play a significant role in the susceptibility to EOC.

Andrusiek, D. L., Szydlo, D., May, S., Brasel, K. J., Minei, J., Van Heest, R., et al. (2015). A comparison of invasive airway management and rates of pneumonia in prehospital and hospital settings. *Prehospital Emergency Care, 19*(4), 475-481.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, linalyl isovalerate, CAS registry number 1118-27-0. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Reproductive toxicity was based on the Threshold of Toxicological Concern (TTC) of 0.03 mg/kg/day for a Cramer Class I material. The estimated systemic exposure is determined to be equal to this value while assuming 100% absorption from skin contact and inhalation. A systemic exposure at or below the TTC value is acceptable.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, fenchyl alcohol, CAS registry number 1632-73-1. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 15 mg/kg/day. A gavage 13-week subchronic toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 10,714 while assuming 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, alpha-butylcinnamaldehyde, CAS registry number 7492-44-6. *Food*

and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined to have the most conservative systemic exposure derived NO[A]EL of 29.9 mg/kg/day. A dietary 14-week subchronic toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 3784810 while considering 9.54% absorption from skin contact and 100% from inhalation. A MOE of > 100 is deemed acceptable.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, benzyl alcohol, CAS registry number 100-51-6. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Arao, R. F., Rosenberg, K. D., McWeeney, S., & Hedberg, K. (2015). Influenza vaccination of pregnant women: Attitudes and behaviors of oregon physician prenatal care providers. *Maternal and Child Health Journal, 19*(4), 783-789.

Arkind, J., Likumahuwa-Ackman, S., Warren, N., Dickerson, K., Robbins, L., Norman, K., et al. (2015). Lessons learned from developing a patient engagement panel: An OCHIN report. *Journal of the American Board of Family Medicine : JABFM, 28*(5), 632-638.

There is renewed interest in patient engagement in clinical and research settings, creating a need for documenting and publishing lessons learned from efforts to meaningfully engage patients. This article describes early lessons learned from the development of OCHIN's Patient Engagement Panel (PEP). OCHIN supports a national network of more than 300 community health centers (CHCs) and other primary care settings that serve over 1.5 million patients annually across nearly 20 states. The PEP was conceived in 2009 to harness the CHC tradition of patient engagement in this new era of patient-centered outcomes research and to ensure that patients were engaged throughout the life cycle of our research projects, from conception to

dissemination. Developed by clinicians and researchers within our practice-based research network, recruitment of patients to serve as PEP members began in early 2012. The PEP currently has a membership of 18 patients from 3 states. Over the past 24 months, the PEP has been involved with 12 projects. We describe developing the PEP and challenges and lessons learned (eg, recruitment, funding model, creating value for patient partners, compensation). These lessons learned are relevant not only for research but also for patient engagement in quality improvement efforts and other clinical initiatives.

Arnold, B., Elliott, A., Laohamroonvorapongse, D., Hanna, J., Norvell, D., & Koh, J. (2015). Autistic children and anesthesia: Is their perioperative experience different? *Paediatric Anaesthesia,* BACKGROUND: Children with autism spectrum disorders (ASD) are an increasingly common patient population in the perioperative setting. Children with ASD present with abnormal development in social interaction, communication, and stereotyped patterns of behavior and may be more prone to elevated perioperative anxiety. The perioperative experience for these patients is complex and presents a unique challenge for clinicians. AIM: The aim of the current study was to provide a further understanding of the premedication patterns and perioperative experiences of children with ASD in comparison to children without ASD. METHODS: Using a retrospective cohort study design, medical records were evaluated for patients with and without ASD undergoing general anesthesia for dental rehabilitation from 2006-2011. The following objectives were measured and compared: (i) premedication patterns and (ii) complications, pain, anesthetic type, PACU time, and time to discharge. To compare categorical variables, the chi-square test was used. Bivariate and multivariable analyses were performed to control for potential confounding as a result of baseline differences between the two groups. RESULTS: A total of 121 ASD patients and 881 non-ASD patients were identified. When controlling for age, weight, and gender, children in the ASD group were more likely to have nonstandard premedication types ($P < 0.0001$), while children without ASD were more likely to have standard premedication types ($P < 0.0001$). No significant group differences were identified in regards to the other outcome measures. CONCLUSIONS: Other than a significant difference in the premedication type and route, we found that children with ASD seemed to have similar perioperative experiences as non-ASD subjects. It was especially interesting to find that their postoperative period did not pose any

special challenges. There is much to be learned about this unique patient population, and a more in-depth prospective evaluation is warranted to help better delineate the best approach to caring for these patients.

Ashjian, E., Salamin, L. B., Eschenburg, K., Kraft, S., & Mackler, E. (2015). Evaluation of outpatient medication reconciliation involving student pharmacists at a comprehensive cancer center. *Journal of the American Pharmacists Association, 55*(5), 540-545.

Aspinwall, L. G., Stump, T. K., Taber, J. M., Kohlmann, W., Leaf, S. L., & Leachman, S. A. (2015). Impact of melanoma genetic test reporting on perceived control over melanoma prevention. *Journal of Behavioral Medicine, 38*(5), 754-765.

Asplund, K. M., Kair, L. R., Arain, Y. H., Cervantes, M., Oreskovic, N. M., & Zuckerman, K. E. (2015). Early childhood screen time and parental attitudes toward child television viewing in a low-income latino population attending the special supplemental nutrition program for women, infants, and children. *Childhood Obesity (Print),*

BACKGROUND: Early childhood media exposure is associated with obesity and multiple adverse health conditions. The aims of this study were to assess parental attitudes toward childhood television (TV) viewing in a low-income population and examine the extent to which child BMI, child/parent demographics, and household media environment are associated with adherence to American Academy of Pediatrics (AAP) guidelines for screen time. METHODS: This was a cross-sectional survey study of 314 parents of children ages 0-5 years surveyed in English or Spanish by self-administered questionnaire at a Special Supplemental Nutrition Program for Women, Infants and Children (WIC) clinic in Oregon. RESULTS: In this majority Latino sample (73%), half (53%) of the children met AAP guidelines on screen time limits, 56% met AAP guidelines for no TV in the child's bedroom, and 29% met both. Children were more likely to meet AAP guidelines when there were <2 TVs in the home, there was no TV during dinner, or their parents spent less time viewing electronic media. Parents who spent less time viewing electronic media were more likely to report believing that TV provides little value or usefulness. CONCLUSIONS: In this low-income, predominantly Latino population attending WIC, parent media-viewing and household

media environment are strongly associated with child screen time. Programs aimed at reducing child screen time may benefit from interventions that address parental viewing habits.

Babaeian, A., Bayestehtashk, A., & Bandarabadi, M. (2015). Multiple manifold clustering using curvature constrained path. *PloS One, 10*(9), e0137986.

The problem of multiple surface clustering is a challenging task, particularly when the surfaces intersect. Available methods such as Isomap fail to capture the true shape of the surface near by the intersection and result in incorrect clustering. The Isomap algorithm uses shortest path between points. The main draw back of the shortest path algorithm is due to the lack of curvature constrained where causes to have a path between points on different surfaces. In this paper we tackle this problem by imposing a curvature constraint to the shortest path algorithm used in Isomap. The algorithm chooses several landmark nodes at random and then checks whether there is a curvature constrained path between each landmark node and every other node in the neighborhood graph. We build a binary feature vector for each point where each entry represents the connectivity of that point to a particular landmark. Then the binary feature vectors could be used as a input of conventional clustering algorithm such as hierarchical clustering. We apply our method to simulated and some real datasets and show, it performs comparably to the best methods such as K-manifold and spectral multi-manifold clustering.

Babwah, A. V., Navarro, V. M., Ahow, M., Pampillo, M., Nash, C., Fayazi, M., et al. (2015). GnRH neuron-specific ablation of Galphaq/11 results in only partial inactivation of the neuroendocrine-reproductive axis in both male and female mice: In vivo evidence for Kiss1r-coupled Galphaq/11-independent GnRH secretion. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 35*(37), 12903-12916.

The gonadotropin-releasing hormone (GnRH) is the master regulator of fertility and kisspeptin (KP) is a potent trigger of GnRH secretion from GnRH neurons. KP signals via KISS1R, a Galphaq/11-coupled receptor, and mice bearing a global deletion of Kiss1r (Kiss1r(-/-)) or a GnRH neuron-specific deletion of Kiss1r (Kiss1r(d/d)) display hypogonadotropic hypogonadism and infertility. KISS1R also signals via beta-arrestin, and in mice lacking beta-arrestin-1 or -2, KP-triggered GnRH secretion is significantly diminished. Based on these findings, we

hypothesized that ablation of Galphaq/11 in GnRH neurons would diminish but not completely block KP-triggered GnRH secretion and that Galphaq/11-independent GnRH secretion would be sufficient to maintain fertility. To test this, Gnaq (encodes Galphaq) was selectively inactivated in the GnRH neurons of global Gna11 (encodes Galpha11)-null mice by crossing Gnrh-Cre and Gnaq(fl/fl);Gna11(-/-) mice. Experimental Gnaq(fl/fl);Gna11(-/-);Gnrh-Cre (Gnaq(d/d)) and control Gnaq(fl/fl);Gna11(-/-) (Gnaq(fl/fl)) littermate mice were generated and subjected to reproductive profiling. This process revealed that testicular development and spermatogenesis, preputial separation, and anogenital distance in males and day of vaginal opening and of first estrus in females were significantly less affected in Gnaq(d/d) mice than in previously characterized Kiss1r(-/-) or Kiss1r(d/d) mice. Additionally, Gnaq(d/d) males were subfertile, and although Gnaq(d/d) females did not ovulate spontaneously, they responded efficiently to a single dose of gonadotropins. Finally, KP stimulation triggered a significant increase in gonadotropins and testosterone levels in Gnaq(d/d) mice. We therefore conclude that the milder reproductive phenotypes and maintained responsiveness to KP and gonadotropins reflect Galphaq/11-independent GnRH secretion and activation of the neuroendocrine-reproductive axis in Gnaq(d/d) mice. SIGNIFICANCE STATEMENT: The gonadotropin-releasing hormone (GnRH) is the master regulator of fertility. Over the last decade, several studies have established that the KISS1 receptor, KISS1R, is a potent trigger of GnRH secretion and inactivation of KISS1R on the GnRH neuron results in infertility. While KISS1R is best understood as a Galphaq/11-coupled receptor, we previously demonstrated that it could couple to and signal via non-Galphaq/11-coupled pathways. The present study confirms these findings and, more importantly, while it establishes Galphaq/11-coupled signaling as a major conduit of GnRH secretion, it also uncovers a significant role for non-Galphaq/11-coupled signaling in potentiating reproductive development and function. This study further suggests that by augmenting signaling via these pathways, GnRH secretion can be enhanced to treat some forms of infertility.

Balasubramanian, B. A., Fernald, D., Dickinson, L. M., Davis, M., Gunn, R., Crabtree, B. F., et al. (2015). REACH of interventions integrating primary care and behavioral health. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S73-85.

PURPOSE: This study reports REACH (the extent to which an intervention or program was

delivered to the identified target population) of interventions integrating primary care and behavioral health implemented by real-world practices. METHODS: Eleven practices implementing integrated care interventions provided data to calculate REACH as follows: 1) Screening REACH defined as proportion of target patients assessed for integrated care, and 2) Integrated care services REACH-defined as proportion of patients receiving integrated services of those who met specific criteria. Difference in mean REACH between practices was evaluated using t test. RESULTS: Overall, 26.2% of target patients (n = 24,906) were assessed for integrated care and 41% (n = 836) of eligible patients received integration services. Practices that implemented systematic protocols to identify patients needing integrated care had a significantly higher screening REACH (mean, 70%; 95% CI [confidence interval], 46.6-93.4%) compared with practices that used clinicians' discretion (mean, 7.9%; 95% CI, 0.6-15.1; P = .0014). Integrated care services REACH was higher among practices that used clinicians' discretion compared with those that assessed patients systematically (mean, 95.8 vs 53.8%; P = .03). CONCLUSION: REACH of integrated care interventions differed by practices' method of assessing patients. Measuring REACH is important to evaluate the extent to which integration efforts affect patient care and can help demonstrate the impact of integrated care to payers and policy makers.

Barbosa, C., Bray, J. W., Dowd, W. N., Mills, M. J., Moen, P., Wipfli, B., et al. (2015). Return on investment of a work-family intervention: Evidence from the work, family, and health network. *Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine, 57*(9), 943-951.

OBJECTIVE: To estimate the return on investment (ROI) of a workplace initiative to reduce work-family conflict in a group-randomized 18-month field experiment in an information technology firm in the United States. METHODS: Intervention resources were micro-costed; benefits included medical costs, productivity (presenteeism), and turnover. Regression models were used to estimate the ROI, and cluster-robust bootstrap was used to calculate its confidence interval. RESULTS: For each participant, model-adjusted costs of the intervention were $690 and company savings were $1850 (2011 prices). The ROI was 1.68 (95% confidence interval, -8.85 to 9.47) and was robust in sensitivity analyses. CONCLUSION: The positive ROI indicates that employers' investment in an intervention to reduce work-family conflict can enhance their business. Although

this was the first study to present a confidence interval for the ROI, results are comparable with the literature.

Barr, T., Helms, C., Grant, K., & Messaoudi, I. (2015). Opposing effects of alcohol on the immune system. *Progress in Neuro-Psychopharmacology & Biological Psychiatry,*

Several studies have described a dose-dependent effect of alcohol on human health with light to moderate drinkers having a lower risk of all-cause mortality than abstainers, while heavy drinkers are at the highest risk. In the case of the immune system, moderate alcohol consumption is associated with reduced inflammation and improved responses to vaccination, while chronic heavy drinking is associated with a decreased frequency of lymphocytes and increased risk of both bacterial and viral infections. However, the mechanisms by which alcohol exerts a dose-dependent effect on the immune system remain poorly understood due to a lack of systematic studies that examine the effect of multiple doses and different time courses. This review will summarize our current understanding of the impact of moderate versus excessive alcohol consumption on the innate and adaptive branches of the immune system derived from both in vitro as well as in vivo studies carried out in humans and animal model studies.

Basraon, S. K., Mele, L., Myatt, L., Roberts, J. M., Hauth, J. C., Leveno, K. J., et al. (2015). Relationship of early pregnancy waist-to-hip ratio versus body mass index with gestational diabetes mellitus and insulin resistance. *American Journal of Perinatology,*

Objective To determine the risk of gestational diabetes mellitus (GDM) and insulin resistance (IR) in obesity defined by body mass index (BMI), waist-to-hip ratio (WHR), or both combined. Methods Secondary analysis of a randomized multicenter trial of antioxidant supplementation versus placebo in nulliparous low-risk women to prevent pregnancy associated hypertension. Women between 9 and 16 weeks with data for WHR and BMI were analyzed for GDM (n = 2,300). Those with fasting glucose and insulin between 22 and 26 weeks (n = 717) were analyzed for IR by homeostatic model assessment of IR (normal, /= 0.85; BMI >/= 30 kg/m2). Receiver operating characteristic curves and logistic regression models were used. Results Compared with normal, the risks of GDM or IR were higher in obese by BMI or WHR. The subgroup with obesity by WHR but not by BMI had no increased risk of GDM. BMI was a better

predictor of IR (area under the curve [AUC]: 0.71 [BMI], 0.65 [WHR], p = 0.03) but similar to WHR for GDM (AUC: 0.68 [BMI], 0.63 [WHR], p = 0.18). Conclusion Increased WHR and BMI in early pregnancy are associated with IR and GDM. BMI is a better predictor of IR compared with WHR. Adding WHR to BMI does not improve its ability to detect GDM or IR.

Beadell, N. C., Bazan, T., & Lutsep, H. (2015). The year embolectomy won: A review of five trials assessing the efficacy of mechanical intervention in acute stroke. *Current Cardiology Reports, 17*(11), 102-015-0657-x.

Embolectomy with stentriever devices is the newest treatment for acute stroke. Since 1995, treatment of acute stroke has been limited to a 4.5-h window with the use of intravenous tissue plasminogen activator (tPA). Five articles have been published in 2015 with the results supporting the paired treatment of tPA and embolectomy. This has also expanded the treatment window to greater than 4.5 h and produced evidence which will guide selection of patients that will benefit most from this therapy. This article will compare and contrast this most recent evidence.

Bee, Y. -., Alonzo, B., & Ng, J. D. (2015). Review of AlloDerm acellular human dermis regenerative tissue matrix in multiple types of oculofacial plastic and reconstructive surgery. *Ophthalmic Plastic and Reconstructive Surgery, 31*(5), 348-351.

Bennett, W. M., Batiuk, T. D., McEvoy, K. M., Douzdjian, V., Hyde, J., Shaut, C., et al. (2015). Early post-transplant lymphoproliferative disease in the donor ureter without systemic involvement: A case report. *Transplantation Proceedings, 47*(7), 2301-2303.

BACKGROUND: Post-transplant lymphoproliferative disease is a serious complication of renal transplantation. Major risk factors include Epstein-Barr virus (EBV) seronegativity and induction immunosuppression with lymphocyte-depleting agents. RESULTS: We present a case of a 50-year year-old woman with very early onset PTLD confined to the donor ureter. Phenotypic studies on the tumor material reveal that the lymphoma was most likely of donor origin. A complete staging workup including the kidney allograft was negative for any other sites of involvement. CONCLUSIONS: This case, which had a fatal outcome, emphasizes the risk of renal transplantation in BV-negative individuals when given induction with lymphocyte-depleting drugs.

Benninger, B. (2015). *The accessory nerve (CN XI)*

Berinstein, N. L., Karkada, M., Oza, A. M., Odunsi, K., Villella, J. A., Nemunaitis, J. J., et al. (2015). Survivin-targeted immunotherapy drives robust polyfunctional T cell generation and differentiation in advanced ovarian cancer patients. *Oncoimmunology, 4*(8)

Bidwell, J. T., Vellone, E., Lyons, K. S., D'Agostino, F., Riegel, B., Juarez-Vela, R., et al. (2015). Determinants of heart failure self-care maintenance and management in patients and caregivers: A dyadic analysis. *Research in Nursing & Health, 38*(5), 392-402.

Disease self-management is a critical component of maintaining clinical stability for patients with chronic illness. This is particularly evident in the context of heart failure (HF), which is the leading cause of hospitalization for older adults. HF self-management, commonly known as HF self-care, is often performed with the support of informal caregivers. However, little is known about how a HF dyad manages the patient's care together. The purpose of this study was to identify determinants of patient and caregiver contributions to HF self-care maintenance (daily adherence and symptom monitoring) and management (appropriate recognition and response to symptoms), utilizing an approach that controls for dyadic interdependence. This was a secondary analysis of cross-sectional data from 364 dyads of Italian HF patients and caregivers. Multilevel modeling was used to identify determinants of HF self-care within patient-caregiver dyads. Patients averaged 76.2 (SD = 10.7) years old, and a slight majority (56.9%) was male, whereas caregivers averaged 57.4 (SD = 14.6) years old, and about half (48.1%) were male. Most caregivers were adult children (48.4%) or spouses (32.7%) of patients. Both patients and caregivers reported low levels of HF maintenance and management behaviors. Significant individual and dyadic determinants of self-care maintenance and self-care management included gender, quality of life, comorbid burden, impaired ADLs, cognition, hospitalizations, HF duration, relationship type, relationship quality, and social support. These comprehensive dyadic models assist in elucidating the complex nature of patient-caregiver relationships and their influence on HF self-care, leading to more effective ways to intervene and optimize outcomes. (c) 2015 Wiley Periodicals, Inc.

Broeckel, R., Haese, N., Messaoudi, I., & Streblow, D. N. (2015). Nonhuman primate models of chikungunya virus infection and disease (CHIKV NHP model). *Pathogens (Basel, Switzerland), 4*(3), 662-681.

Chikungunya virus (CHIKV) is a positive-sense RNA virus transmitted by Aedes mosquitoes. CHIKV is a reemerging Alphavirus that causes acute febrile illness and severe and debilitating polyarthralgia of the peripheral joints. Huge epidemics and the rapid spread of CHIKV seen in India and the Indian Ocean region established CHIKV as a global health concern. This concern was further solidified by the recent incursion of the virus into the Western hemisphere, a region without pre-existing immunity. Nonhuman primates (NHPs) serve as excellent animal models for understanding CHIKV pathogenesis and pre-clinical assessment of vaccines and therapeutics. NHPs present advantages over rodent models because they are a natural amplification host for CHIKV and they share significant genetic and physiological homology with humans. CHIKV infection in NHPs results in acute fever, rash, viremia and production of type I interferon. NHPs develop CHIKV-specific B and T-cells, generating neutralizing antibodies and CHIKV-specific CD4(+) and CD8(+) T-cells. CHIKV establishes a persistent infection in NHPs, particularly in cynomolgus macaques, because infectious virus could be recovered from spleen, liver, and muscle as late as 44 days post infection. NHPs are valuable models that are useful in preclinical testing of vaccines and therapeutics and uncovering the details of CHIKV pathogenesis.

Bronson, N. W., Diggs, B. S., Bakis, G., Gatter, K. M., Sheppard, B. C., Hunter, J. G., et al. (2015). Molecular marker expression is highly heterogeneous in esophageal adenocarcinoma and does not predict a response to neoadjuvant therapy. *Journal of Gastrointestinal Surgery : Official Journal of the Society for Surgery of the Alimentary Tract,*

A reliable method to identify pathologic complete responders (pCR) or non-responders (NR) to neoadjuvant chemoradiation therapy (NAT) would dramatically improve therapy for esophageal cancer. The purpose of this study is to investigate if a distinct profile of prognostic molecular markers can predict pCR after neoadjuvant therapy. Expression of p53, Her-2/neu, Cox-2, Beta-catenin, E-cadherin, MMP-1, NFkB, and TGF-B was measured by immunohistochemistry in pre-treatment biopsy tissue and graded by an experienced pathologist. A pCR was defined as no evidence of malignancy on final pathology. Molecular profiles comparing responders to non-

responders were analyzed using classification and regression tree analysis to investigate response to NAT and overall survival. Nineteen patients were pCRs and 34 were NRs. pCRs were more likely to be alive at follow-up than NRs ($p < 0.01$). Thirty-seven distinct profiles were identified. Expression of molecular markers was highly heterogeneous between patients and did not correlate with a response to NAT, survival ($p = 0.47$) or clinical stage ($p = 0.39$) when evaluated either as individual markers or in combination with other expression patterns. NAT dramatically impacts survival through a mechanism independent of known molecular markers of esophageal cancer, which are expressed in a highly heterogeneous fashion and do not predict response to NAT or survival.

Brower, A., Trefz, L., & Burns, C. (2015). Implementing the use of chemical-free products in a perinatal unit. *JOGNN - Journal of Obstetric, Gynecologic, and Neonatal Nursing, 44*(5), 644-653.

Buss, C., Graham, A. M., Rasmussen, J., Entringer, S., Gilmore, J. H., Styner, M., et al. (2015). Lack of maternal stress dampening during pregnancy is associated with altered neonatal amygdala connectivity. *Psychoneuroendocrinology, 61*, 11-12.

Butler, T. M., Johnson-Camacho, K., Peto, M., Wang, N. J., Macey, T. A., Korkola, J. E., et al. (2015). Exome sequencing of cell-free DNA from metastatic cancer patients identifies clinically actionable mutations distinct from primary disease. *PloS One, 10*(8), e0136407.

The identification of the molecular drivers of cancer by sequencing is the backbone of precision medicine and the basis of personalized therapy; however, biopsies of primary tumors provide only a snapshot of the evolution of the disease and may miss potential therapeutic targets, especially in the metastatic setting. A liquid biopsy, in the form of cell-free DNA (cfDNA) sequencing, has the potential to capture the inter- and intra-tumoral heterogeneity present in metastatic disease, and, through serial blood draws, track the evolution of the tumor genome. In order to determine the clinical utility of cfDNA sequencing we performed whole-exome sequencing on cfDNA and tumor DNA from two patients with metastatic disease; only minor modifications to our sequencing and analysis pipelines were required for sequencing and mutation calling of cfDNA. The first patient had metastatic sarcoma and 47 of 48 mutations present in the primary tumor were also found in the cell-free DNA. The second patient had

metastatic breast cancer and sequencing identified an ESR1 mutation in the cfDNA and metastatic site, but not in the primary tumor. This likely explains tumor progression on Anastrozole. Significant heterogeneity between the primary and metastatic tumors, with cfDNA reflecting the metastases, suggested separation from the primary lesion early in tumor evolution. This is best illustrated by an activating PIK3CA mutation (H1047R) which was clonal in the primary tumor, but completely absent from either the metastasis or cfDNA. Here we show that cfDNA sequencing supplies clinically actionable information with minimal risks compared to metastatic biopsies. This study demonstrates the utility of whole-exome sequencing of cell-free DNA from patients with metastatic disease. cfDNA sequencing identified an ESR1 mutation, potentially explaining a patient's resistance to aromatase inhibition, and gave insight into how metastatic lesions differ from the primary tumor.

Butterfield, C. N., Tao, L., Chacon, K. N., Spiro, T. G., Blackburn, N. J., Casey, W. H., et al. (2015). Multicopper manganese oxidase accessory proteins bind cu and heme. *Biochimica Et Biophysica Acta,*

Multicopper oxidases (MCOs) catalyze the oxidation of a diverse group of metal ions and organic substrates by successive single-electron transfers to O2 via four bound Cu ions. MnxG, which catalyzes MnO2 mineralization by oxidizing both Mn(II) and Mn(III), is unique among multicopper oxidases in that it carries out two energetically distinct electron transfers and is tightly bound to accessory proteins. There are two of these, MnxE and MnxF, both approximately 12kDa. Although their sequences are similar to those found in the genomes of several Mn-oxidizing Bacillus species, they are dissimilar to those of proteins with known function. Here, MnxE and MnxF are co-expressed independent of MnxG and are found to oligomerize into a higher order stoichiometry, likely a hexamer. They bind copper and heme, which have been characterized by electron paramagnetic resonance (EPR), X-ray absorption spectroscopy (XAS), and UV-visible (UV-vis) spectrophotometry. Cu is found in two distinct type 2 (T2) copper centers, one of which appears to be novel; heme is bound as a low-spin species, implying coordination by two axial ligands. MnxE and MnxF do not oxidize Mn in the absence of MnxG and are the first accessory proteins to be required by an MCO. This may indicate that Cu and heme play roles in electron transfer and/or Cu trafficking.

Cantor, A. G., Bougatsos, C., & McDonagh, M. (2015). In response. *Annals of Internal Medicine, 163*(5), 400.

Carbonaro, T. M., Eshleman, A. J., Forster, M. J., Cheng, K., Rice, K. C., & Gatch, M. B. (2015). The role of 5-HT2A, 5-HT2C and mGlu2 receptors in the behavioral effects of tryptamine hallucinogens N,N-dimethyltryptamine and N,N-diisopropyltryptamine in rats and mice. *Psychopharmacology, 232*(1), 275-284.

Carbone, L., & Chavez, S. L. (2015). Mammalian pre-implantation chromosomal instability: Species comparison, evolutionary considerations, and pathological correlations. *Systems Biology in Reproductive Medicine,* , 1-15.

Pre-implantation embryo development in mammals begins at fertilization with the migration and fusion of the maternal and paternal pro-nuclei, followed by the degradation of inherited factors involved in germ cell specification and the activation of embryonic genes required for subsequent cell divisions, compaction, and blastulation. The majority of studies on early embryogenesis have been conducted in the mouse or non-mammalian species, often requiring extrapolation of the findings to human development. Given both conserved similarities and species-specific differences, however, even comparison between closely related mammalian species may be challenging as certain aspects, including susceptibility to chromosomal aberrations, varies considerably across mammals. Moreover, most human embryo studies are limited to patient samples obtained from in vitro fertilization (IVF) clinics and donated for research, which are generally of poorer quality and produced with germ cells that may be sub-optimal. Recent technical advances in genetic, epigenetic, chromosomal, and time-lapse imaging analyses of high quality whole human embryos have greatly improved our understanding of early human embryogenesis, particularly at the single embryo and cell level. This review summarizes the major characteristics of mammalian pre-implantation development from a chromosomal perspective, in addition to discussing the technological achievements that have recently been developed to obtain this data. We also discuss potential translation to clinical applications in reproductive medicine and conclude by examining the broader implications of these findings for the evolution of mammalian species and cancer pathology in somatic cells.

Carim-Todd, L., Mitchell, S. H., & Oken, B. S. (2015). Impulsivity and stress response in non-dependent smokers (tobacco chippers) in comparison to heavy smokers and non-smokers. *Nicotine & Tobacco Research : Official Journal of the Society for Research on Nicotine and Tobacco,*

INTRODUCTION: Tobacco chippers are light smokers with stable patterns of smoking that exhibit lower nicotine dependence severity than heavy smokers. Chippers may provide valuable information about the factors influencing drug dependence. Impulsivity and stress are two factors known to influence smoking. By comparing non-dependent smokers (tobacco chippers, n=25) to dependent smokers (heavy smokers, n=23) and non-smokers (n=25), this study examines the relationship between nicotine dependence, impulsivity, chronic stress, and stress reactivity. METHODS: A total of 73 adult participants completed a study visit that included questionnaires to measure nicotine dependence, chronic stress, personality, affect, withdrawal, and craving. Impulsivity was measured with the delay discounting task and the flanker task. Stress reactivity was assessed by monitoring respiration, heart rate, and salivary cortisol during performance of a titrated Stroop task. Effects of acute stress on affect and craving were examined. RESULTS: Tobacco chippers were as impulsive as heavy smokers on the delay discounting task but no different from non-smokers on the flanker task. Heavy smokers reported higher perceived stress than chippers and non-smokers. Perceived stress was a significant predictor of discounting only in heavy smokers. Acute stress induced changes in respiration, heart rate, and heart rate variability. Craving and negative affect increased after stress in both smoking groups, but craving was associated with affect only in chippers. CONCLUSIONS: Tobacco chippers do not differ from heavy smokers in impulsivity, but do differ in perceived stress. One's perception and experience of stress might be associated to nicotine dependence resistance and could inform smoking cessation treatments.

Carter-O'Connell, I., & Cohen, M. S. (2015). Identifying direct protein targets of poly-ADP-ribose polymerases (PARPs) using engineered PARP variants-orthogonal nicotinamide adenine dinucleotide (NAD+) analog pairs. *Current Protocols in Chemical Biology, 7*, 121-139.

Poly-ADP-ribose polymerases (PARPs) comprise a family of 17 distinct enzymes that catalyze the transfer of ADP-ribose from nicotinamide adenine dinucleotide (NAD+) to acceptor sites on

protein targets. PARPs have been implicated in a number of essential signaling pathways regulating both normal cell function and pathophysiology. To understand the physiological role of each PARP family member in the cell we need to identify the direct targets for each unique PARP in a cellular context. PARP-family member-specific target identification is challenging because of their shared catalytic mechanism and functional redundancy. To address this challenge, we have engineered a PARP variant that efficiently uses an orthogonal NAD+ analog, an analog that endogenous PARPs cannot use, as a substrate for ADP-ribosylation. The protocols in this unit describe a general procedure for using engineered PARP variants-orthogonal NAD+ analog pairs for labeling and identifying the direct targets of the poly-subfamily of PARPs (PARPs 1-3, 5, and 6). (c) 2015 by John Wiley & Sons, Inc.

Castle, J. R., El Youssef, J., Bakhtiani, P. A., Cai, Y., Stobbe, J. M., Branigan, D., et al. (2015). Effect of repeated glucagon doses on hepatic glycogen in type 1 diabetes: Implications for a bihormonal closed-loop system. *Diabetes Care,*

OBJECTIVE: To evaluate subjects with type 1 diabetes for hepatic glycogen depletion after repeated doses of glucagon, simulating delivery in a bihormonal closed-loop system. RESEARCH DESIGN AND METHODS: Eleven adult subjects with type 1 diabetes participated. Subjects underwent estimation of hepatic glycogen using 13C MRS. MRS was performed at the following four time points: fasting and after a meal at baseline, and fasting and after a meal after eight doses of subcutaneously administered glucagon at a dose of 2 microg/kg, for a total mean dose of 1,126 microg over 16 h. The primary and secondary end points were, respectively, estimated hepatic glycogen by MRS and incremental area under the glucose curve for a 90-min interval after glucagon administration. RESULTS: In the eight subjects with complete data sets, estimated glycogen stores were similar at baseline and after repeated glucagon doses. In the fasting state, glycogen averaged 21 +/- 3 g/L before glucagon administration and 25 +/- 4 g/L after glucagon administration (mean +/- SEM, P = NS). In the fed state, glycogen averaged 40 +/- 2 g/L before glucagon administration and 34 +/- 4 g/L after glucagon administration (P = NS). With the use of an insulin action model, the rise in glucose after the last dose of glucagon was comparable to the rise after the first dose, as measured by the 90-min incremental area under the glucose curve. CONCLUSIONS: In adult subjects with well-controlled type 1 diabetes (mean A1C 7.2%),

glycogen stores and the hyperglycemic response to glucagon administration are maintained even after receiving multiple doses of glucagon. This finding supports the safety of repeated glucagon delivery in the setting of a bihormonal closed-loop system.

Centeno, C. J., Al-Sayegh, H., Bashir, J., Goodyear, S., & Freeman, M. D. (2015). A dose response analysis of a specific bone marrow concentrate treatment protocol for knee osteoarthritis. *BMC Musculoskeletal Disorders, 16*(1), 258-015-0714-z.

BACKGROUND: Prior studies describing the treatment of symptomatic knee osteoarthritis with injections of bone marrow concentrate have provided encouraging results. The relationship between the cellular dose contained within the bone marrow concentrate and efficacy of the treatment, however, is unclear. In the present study we describe clinical outcomes for symptomatic knee osteoarthritis in relation to higher and lower cell concentrations contained within a bone marrow concentrate treatment protocol. METHODS: Data from an ongoing patient registry was culled to identify 373 patients that received bone marrow concentrate injections for the treatment of 424 osteoarthritic knee joints. The clinical scales for these patients were assessed at baseline and then tracked post-procedure at 1, 3, 6 and 12 months, and annually thereafter. Tracked outcomes included the numeric pain scale; a lower extremity functional questionnaire; an International Knee Documentation Committee scale; and a subjective improvement rating scale. Using pain and functional outcome measures, a receiver operating characteristic analysis was used to define an optimal clinical outcome threshold at which bone marrow nucleated cell count could be divided into either a lower or higher cell count group within a treatment protocol. RESULTS: The lower and higher cell count groups were defined using a threshold of 4 x 10(8) cells. There were 224 and 185 knee joints treated in the lower (4 x 10(8)) cell count groups respectively. Most joints were diagnosed with early stage knee osteoarthritis. Both the lower and higher cell count groups demonstrated significant positive results with the treatment for all of the pain and functional metrics. The higher cell count group reported lower post treatment numeric pain scale values, in comparison with the lower cell count group (1.6 vs. 3.2; $P < 0.001$). No significant differences were detected for the other metrics, however. CONCLUSIONS: Improved function and reduced pain was observed in patients treated with a bone marrow concentrate protocol regardless of cellular dose; however, patients receiving a

higher concentration of cells reported a better pain outcome in comparison with the lower dose group. These preliminary findings suggest that cell dose may be an important factor governing clinical outcomes in autologous bone marrow concentrate treatment of knee osteoarthritis. Further studies using a larger patient population may help elucidate these findings.

Chakraborty, S., Polen, M. J., Chacon, K. N., Wilson, T. D., Yu, Y., Reed, J., et al. (2015). Binuclear cu formation in biosynthetic models of cu in azurin proceeds via a novel cu(cys)his mononuclear copper intermediate. *Biochemistry,*

CuA is a binuclear electron transfer (ET) center found in cytochrome c oxidases (CcOs), nitrous oxide reductases (N2ORs), and nitric oxide reductase (NOR). In these proteins, the CuA centers facilitate efficient ET (kET > 104 s-1) under low thermodynamic driving forces (10-90 mV). While the structure and functional properties of CuA are well understood, a detailed mechanism of the incorporation of copper into the protein and the identity of the intermediates formed during the CuA maturation process are still lacking. Previous studies of the CuA assembly mechanism in vitro using a biosynthetic model CuA center in azurin (CuAAz) identified a novel intermediate X (Ix) during reconstitution of the binuclear site. However, because of the instability of Ix and the coexistence of other Cu centers, such as CuA' and type 1 copper centers, the identity of this intermediate could not be established. Here, we report the mechanism of CuA assembly using variants of Glu114XCuAAz (X = Gly, Ala, Leu, or Gln), the backbone carbonyl of which acts as a ligand to the CuA site, with a major focus on characterization of the novel intermediate Ix. We show that CuA assembly in these variants proceeds through several types of Cu centers, such as mononuclear red type 2 Cu, the novel intermediate Ix, and blue type 1 Cu. Our results show that the backbone flexibility of the Glu114 residue is an important factor in determining the rates of T2Cu --> Ix formation, suggesting that CuA formation is facilitated by swinging of the ligand loop, which internalizes the T2Cu capture complex to the protein interior. The kinetic data further suggest that the nature of the Glu114 side chain influences the time scales on which these intermediates are formed, the wavelengths of the absorption peaks, and how cleanly one intermediate is converted to another. Through careful understanding of these mechanisms and optimization of the conditions, we have obtained Ix in approximately 80-85% population in these variants, which allowed us to employ ultraviolet-visible, electron paramagnetic resonance, and

extended X-ray absorption fine structure spectroscopic techniques to identify the Ix as a mononuclear Cu(Cys)2(His) complex. Because some of the intermediates have been proposed to be involved in the assembly of native CuA, these results shed light on the structural features of the important intermediates and mechanism of CuA formation.

Chandran, R., Gardiner, S. K., Fenske, T. S., & Spurgeon, E. S. (2015). Survival trends in T cell prolymphocytic leukemia: A SEER database analysis. *Leukemia and Lymphoma,*

Chang, H., Zhou, Y., Borowsky, A., Barner, K., Spellman, P., & Parvin, B. (2015). Stacked predictive sparse decomposition for classification of histology sections. *International Journal of Computer Vision, 113*(1), 3-18.

Chang, Y. H., Gray, J. W., & Tomlin, C. J. (2014). Exact reconstruction of gene regulatory networks using compressive sensing. *BMC Bioinformatics, 15*, 400-014-0400-4.
BACKGROUND: We consider the problem of reconstructing a gene regulatory network structure from limited time series gene expression data, without any a priori knowledge of connectivity. We assume that the network is sparse, meaning the connectivity among genes is much less than full connectivity. We develop a method for network reconstruction based on compressive sensing, which takes advantage of the network's sparseness. RESULTS: For the case in which all genes are accessible for measurement, and there is no measurement noise, we show that our method can be used to exactly reconstruct the network. For the more general problem, in which hidden genes exist and all measurements are contaminated by noise, we show that our method leads to reliable reconstruction. In both cases, coherence of the model is used to assess the ability to reconstruct the network and to design new experiments. We demonstrate that it is possible to use the coherence distribution to guide biological experiment design effectively. By collecting a more informative dataset, the proposed method helps reduce the cost of experiments. For each problem, a set of numerical examples is presented. CONCLUSIONS: The method provides a guarantee on how well the inferred graph structure represents the underlying system, reveals deficiencies in the data and model, and suggests experimental directions to remedy the deficiencies.

Chase, D. A., Ash, J. S., Cohen, D. J., Hall, J., Olson, G. M., & Dorr, D. A. (2014). The EHR's roles in collaboration between providers: A qualitative study. *AMIA ...Annual Symposium Proceedings / AMIA Symposium.AMIA Symposium, 2014*, 1718-1727.

OBJECTIVE: Examine how the Electronic Health Record (EHR) and its related systems support or inhibit provider collaboration. BACKGROUND: Health care systems in the US are simultaneously implementing EHRs and transitioning to more collaborative delivery systems; this study examines the interaction between these two changes. METHODS: This qualitative study of five US EHR implementations included 49 interviews and over 60 hours of provider observation. We examined the role of the EHR in building relationships, communicating, coordinating, and collaborative decision-making. RESULTS: The EHR plays four roles in collaboration: a repository, a messenger, an orchestrator, and a monitor. While EHR performance varied, common themes were decreased trust due to poor quality documentation, incomplete communication, potential for increased effectiveness through better coordination, and the emerging role of the EHR in identifying performance gaps. CONCLUSION: Both organizational and technical innovations are needed if the EHR is to truly support collaborative behaviors.

Chen, Y., Zhu, W., Zhang, W., Libal, N., Murphy, S. J., Offner, H., et al. (2015). A novel mouse model of thromboembolic stroke. *Journal of Neuroscience Methods, 256*, 203-211.

BACKGROUND: We previously demonstrated that tissue plasminogen activator (tPA) reduces infarct size after mechanical middle cerebral artery occlusion (MCAO) in wild-type (WT) mice and transgenic mice expressing human leukocyte antigen DR2 (DR2-Tg). Clinically, tPA limits ischemic damage by dissolving the clot blocking blood flow through a cerebral artery. To mimic the clinical situation, we developed a new mouse model of thromboembolic stroke, and tested the efficacy of tPA in WT and DR2-Tg mice. New Method Autologous blood is withdrawn into a PE-8 catheter filled with 2 IU alpha-thrombin. After exposing the catheter briefly to air, the catheter is reintroduced into the external (ECA) and advanced into the internal carotid artery (ICA) to allow for intravascular injection of thrombin at the MCA bifurcation. To validate the model, we tested the effect of tPA on laser-Doppler perfusion (LDP) over the MCA territory and infarct size in WT and DR2-Tg mice. RESULTS: The procedure results in a consistent drop in LDP, and leads to a highly reproducible ischemic lesion. When administered at 15min after thrombosis, tPA restored

LDP and resulted in a significant reduction in infarct size at 24h after thrombosis in both WT and DR2-Tg. COMPARISON WITH EXISTING METHODS: Our model significantly reduces surgery time, requires a single anesthesia exposure, and produces a consistent and predictable infarction, with low variability and mortality. CONCLUSION: We validated the efficacy of tPA in restoring blood flow and reducing infarct in a new model of endovascular thromboembolic stroke in the mouse.

Chew, E. Y., Klein, M. L., Clemons, T. E., Agron, E., & Abecasis, G. R. (2015). Reply. *Ophthalmology, 122*(10), e63.

Chew, E. Y., Klein, M. L., Clemons, T. E., Agron, E., & Abecasis, G. R. (2015). Reply. *Ophthalmology, 122*(10), e61-2.

Chew, E. Y., Klein, M. L., Clemons, T. E., Agron, E., & Abecasis, G. R. (2015). Reply. *Ophthalmology, 122*(10), e58-9.

Chiang, J. P., Lamey, T., McLaren, T., Thompson, J. A., Montgomery, H., & De Roach, J. (2015). Progress and prospects of next-generation sequencing testing for inherited retinal dystrophy. *Expert Review of Molecular Diagnostics, 15*(10), 1269-1275.

Next-generation sequencing, also known as massively paralleled sequencing, offers an unprecedented opportunity to study disease mechanisms of inherited retinal dystrophies: a dramatic change from a few years ago. The specific involvement of the retina and the manageable number of genes to sequence make inherited retinal dystrophies an attractive model to study genotype-phenotype correlations. Costs are reducing rapidly and the current overall mutation detection rate of approximately 60% offers real potential for personalized medicine and treatments. This report addresses the challenges ahead, which include: better understanding of the mutation mechanisms of syndromic genes in apparent non-syndromic patients; finding mutations in patients who have tested negative or inconclusive; better variant calling, especially for intronic and synonymous variants; more precise genotype-phenotype correlations and making genetic testing more broadly accessible.

Chou, R., Hashimoto, R., Friedly, J., Fu, R., Bougatsos, C., Dana, T., et al. (2015). Epidural corticosteroid injections for radiculopathy and spinal stenosis: A systematic review and meta-analysis. *Annals of Internal Medicine, 163*(5), 373-381.

Chou, T. H., Delmar, J. A., Wright, C. C., Kumar, N., Radhakrishnan, A., Doh, J. K., et al. (2015). Crystal structure of the mycobacterium tuberculosis transcriptional regulator Rv0302. *Protein Science : A Publication of the Protein Society,*

Mycobacterium tuberculosis is a pathogenic bacterial species, which is neither Gram positive nor Gram negative. It has a unique cell wall, making it difficult to kill and conferring resistance to antibiotics that disrupt cell wall biosynthesis. Thus, the mycobacterial cell wall is critical to the virulence of these pathogens. Recent work shows that the mycobacterial membrane protein large (MmpL) family of transporters contributes to cell wall biosynthesis by exporting fatty acids and lipidic elements of the cell wall. The expression of the Mycobacterium tuberculosis MmpL proteins is controlled by a complicated regulatory network system. Here we report crystallographic structures of two forms of the TetR-family transcriptional regulator Rv0302, which participates in regulating the expression of MmpL proteins. The structures reveal a dimeric, two-domain molecule with architecture consistent with the TetR family of regulators. Comparison of the two Rv0302 crystal structures suggests that the conformational changes leading to derepression may be due to a rigid body rotational motion within the dimer interface of the regulator. Using fluorescence polarization and electrophoretic mobility shift assays, we demonstrate the recognition of promoter and intragenic regions of multiple mmpL genes by this protein. In addition, our isothermal titration calorimetry and electrophoretic mobility shift experiments indicate that fatty acids may be the natural ligand of this regulator. Taken together, these experiments provide new perspectives on the regulation of the MmpL family of transporters.

Cifuentes, M., Davis, M., Fernald, D., Gunn, R., Dickinson, P., & Cohen, D. J. (2015). Electronic health record challenges, workarounds, and solutions observed in practices integrating behavioral health and primary care. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S63-72.

PURPOSE: This article describes the electronic health record (EHR)-related experiences of

practices striving to integrate behavioral health and primary care using tailored, evidenced-based strategies from 2012 to 2014; and the challenges, workarounds and initial health information technology (HIT) solutions that emerged during implementation. METHODS: This was an observational, cross-case comparative study of 11 diverse practices, including 8 primary care clinics and 3 community mental health centers focused on the implementation of integrated care. Practice characteristics (eg, practice ownership, federal designation, geographic area, provider composition, EHR system, and patient panel characteristics) were collected using a practice information survey and analyzed to report descriptive information. A multidisciplinary team used a grounded theory approach to analyze program documents, field notes from practice observation visits, online diaries, and semistructured interviews. RESULTS: Eight primary care practices used a single EHR and 3 practices used 2 different EHRs, 1 to document behavioral health and 1 to document primary care information. Practices experienced common challenges with their EHRs' capabilities to 1) document and track relevant behavioral health and physical health information, 2) support communication and coordination of care among integrated teams, and 3) exchange information with tablet devices and other EHRs. Practices developed workarounds in response to these challenges: double documentation and duplicate data entry, scanning and transporting documents, reliance on patient or clinician recall for inaccessible EHR information, and use of freestanding tracking systems. As practices gained experience with integration, they began to move beyond workarounds to more permanent HIT solutions ranging in complexity from customized EHR templates, EHR upgrades, and unified EHRs. CONCLUSION: Integrating behavioral health and primary care further burdens EHRs. Vendors, in cooperation with clinicians, should intentionally design EHR products that support integrated care delivery functions, such as data documentation and reporting to support tracking patients with emotional and behavioral problems over time and settings, integrated teams working from shared care plans, template-driven documentation for common behavioral health conditions such as depression, and improved registry functionality and interoperability. This work will require financial support and cooperative efforts among clinicians, EHR vendors, practice assistance organizations, regulators, standards setters, and workforce educators.

Cohen, D. J., Balasubramanian, B. A., Davis, M., Hall, J., Gunn, R., Stange, K. C., et al. (2015). Understanding care integration from the ground up: Five organizing constructs that shape integrated practices. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S7-S20.

PURPOSE: To provide empirical evidence on key organizing constructs shaping practical, real-world integration of behavior health and primary care to comprehensively address patients' medical, emotional, and behavioral health needs. METHODS: In a comparative case study using an immersion-crystallization approach, a multidisciplinary team analyzed data from observations of practice operations, interviews, and surveys of practice members, and implementation diaries. Practices were drawn from 2 studies of practices attempting to integrate behavioral health and primary care: Advancing Care Together, a demonstration project of 11 practices located in Colorado, and the Integration Workforce Study, a study of 8 practices across the United States. RESULTS: We identified 5 key organizing constructs influencing integration of primary care and behavioral health: 1) Integration REACH (the extent to which the integration program was delivered to the identified target population), 2) establishment of continuum of care pathways addressing the location of care across the range of patient's severity of illness, 3) approach to patient transitions: referrals or warm handoffs, 4) location of the integration workforce, and 5) participants' mental model for integration. These constructs intertwine within an organization's historic and social context to produce locally adapted approaches to integrating care. Contextual factors, particularly practice type, influenced whether specialty mental health and substance use services were colocated within an organization. CONCLUSION: Interaction among 5 organizing constructs and practice context produces diverse expressions of integrated care. These constructs provide a framework for understanding how primary care and behavioral health services can be integrated in routine practice.

Cohen, D. J., Davis, M., Balasubramanian, B. A., Gunn, R., Hall, J., deGruy, F. V.,3rd, et al. (2015). Integrating behavioral health and primary care: Consulting, coordinating and collaborating among professionals. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S21-31.

PURPOSE: This paper sought to describe how clinicians from different backgrounds interact to deliver integrated behavioral and primary health care, and the contextual factors that shape such

interactions. METHODS: This was a comparative case study in which a multidisciplinary team used an immersion-crystallization approach to analyze data from observations of practice operations, interviews with practice members, and implementation diaries. The observed practices were drawn from 2 studies: Advancing Care Together, a demonstration project of 11 practices located in Colorado; and the Integration Workforce Study, consisting of 8 practices located across the United States. RESULTS: Primary care and behavioral health clinicians used 3 interpersonal strategies to work together in integrated settings: consulting, coordinating, and collaborating (3Cs). Consulting occurred when clinicians sought advice, validated care plans, or corroborated perceptions of a patient's needs with another professional. Coordinating involved 2 professionals working in a parallel or in a back-and-forth fashion to achieve a common patient care goal, while delivering care separately. Collaborating involved 2 or more professionals interacting in real time to discuss a patient's presenting symptoms, describe their views on treatment, and jointly develop a care plan. Collaborative behavior emerged when a patient's care or situation was complex or novel. We identified contextual factors shaping use of the 3Cs, including: time to plan patient care, staffing, employing brief therapeutic approaches, proximity of clinical team members, and electronic health record documenting behavior. CONCLUSION: Primary care and behavioral health clinicians, through their interactions, consult, coordinate, and collaborate with each other to solve patients' problems. Organizations can create integrated care environments that support these collaborations and health professions training programs should equip clinicians to execute all 3Cs routinely in practice.

Cohen, D. M. (2015). Modeling the neurologic and cognitive effects of hyponatremia. *Journal of the American Society of Nephrology : JASN,*

Crawford, J. D., Hsieh, C. M., Schenning, R. C., Slater, M. S., Landry, G. J., Moneta, G. L., et al. (2015). Genetics, pregnancy and aortic degeneration. *Annals of Vascular Surgery,*
We present a case of familial thoracic aortic aneurysm and dissection (FTAAD) in a pregnant female. FTAAD is an inherited, nonsyndromic aortopathy resulting from several genetic mutations critical to aortic wall integrity have been identified. One such mutation is the myosin heavy chain gene (MYH11) which is responsible for 1-2% of all FTAAD cases. This mutation results in aortic

medial degeneration, loss of elastin and reticulin fiber fragmentation predisposing to thoracic aortic aneurysm and dissection. Aortic disease is more aggressive during pregnancy as a result of increased wall stress from hyperdynamic cardiovascular changes and estrogen-induced aortic media degeneration. Our patient was a 29 year old G2P1 woman at 26 weeks gestation presenting with abdominal and back pain. Work-up revealed a 6.4cm ascending aortic aneurysm with a type A dissection extending into all arch vessels, aortic coarctation at the isthmus and a separate focal type B aortic dissection with visceral involvement. Surgical management included concomitant Cesarean-section with delivery of a live premature infant, tubal ligation, ascending aortic replacement with reconstruction of the arch vessels and aortic valve resuspension. The type B dissection was managed medically without complication. This is the first reported case of aortic dissection in a patient with FTAAD/MYH11 mutation and pregnancy. This case highlights that FTAAD and pregnancy cause aortic degeneration via distinct mechanisms and that hyperdynamics of pregnancy increase aortic wall stress. Management of pregnancy associated with aortopathy requires early transfer to a tertiary center, careful investigation to identify familial aortopathy, fetal monitoring and a multidisciplinary team approach.

Cross, C. P., Liao, S., Urdang, Z. D., Srikanth, P., Garinis, A. C., & Steyger, P. S. (2015). Effect of sepsis and systemic inflammatory response syndrome on neonatal hearing screening outcomes following gentamicin exposure. *International Journal of Pediatric Otorhinolaryngology,* OBJECTIVES: Hearing loss in neonatal intensive care unit (NICU) graduates range from 2% to 15% compared to 0.3% in full-term births, and the etiology of this discrepancy remains unknown. The majority of NICU admissions receive potentially ototoxic aminoglycoside therapy, such as gentamicin, for presumed sepsis. Endotoxemia and inflammation are associated with increased cochlear uptake of aminoglycosides and potentiated ototoxicity in mice. We tested the hypothesis that sepsis or systemic inflammatory response syndrome (SIRS) and intravenous gentamicin exposure increases the risk of hearing loss in NICU admissions. METHODS: The Institutional Review Board at Oregon Health & Science University (OHSU) approved this study design. Two hundred and eight infants met initial criteria, and written, informed consent were obtained from parents or guardians of 103 subjects ultimately enrolled in this study. Prospective data from 91 of the enrolled subjects at OHSU Doernbecher Children's Hospital Neonatal Care

Center were processed. Distortion product otoacoustic emissions (DPOAEs; f2 frequency range: 2063-10,031Hz) were obtained prior to discharge to assess auditory performance. To pass the DPOAE screen, normal responses in >6 of 10 frequencies in both ears were required; otherwise the subject was considered a "referral" for a diagnostic hearing evaluation after discharge. Cumulative dosing data and diagnosis of neonatal sepsis or SIRS were obtained from OHSU's electronic health record system, and the data processed to obtain risk ratios. RESULTS: Using these DPOAE screening criteria, 36 (39.5%) subjects would be referred. Seventy-four (81%) subjects had intravenous gentamicin exposure. Twenty (22%) had >/=4 days of gentamicin, and 71 (78%) had /=4 days of gentamicin was 1.92 (p=0.01). Eighteen subjects had sepsis or met neonatal SIRS criteria, 9 of whom had >/=5 days of gentamicin and a DPOAE referral risk ratio of 2.12 (p=0.02) compared to all other subjects. Combining subjects with either vancomycin or furosemide overlap with gentamicin treatment yielded an almost significant risk ratio (RR=1.77, p=0.05) compared to the rest of the cohort. CONCLUSIONS: We report an increased risk of referral with DPOAE screening for those receiving >/=4 days of intravenous gentamicin administration that may contribute to the greater prevalence of hearing loss in NICU graduates. We propose an expanded prospective study to gather a larger cohort of subjects, identifying those with sepsis or neonatal SIRS, to increase the statistical power of this study design. Subsequent studies also need to obtain follow-up diagnostic audiological data to verify whether the outcomes of DPOAE screening, in addition to the standard AABR screen, is a reliable predictor of permanent hearing loss following gentamicin exposure in the NICU.

Cushing, T. A., Roberts, W. O., Hackett, P., Dexter, W. W., Brent, J. S., Young, C. C., et al. (2015). General medical considerations for the wilderness adventurer: Medical conditions that may worsen with or present challenges to coping with wilderness exposure. *Clinical Journal of Sport Medicine : Official Journal of the Canadian Academy of Sport Medicine, 25*(5), 396-403. Participation in wilderness and adventure sports is on the rise, and as such, practitioners will see more athletes seeking clearance to participate in these events. The purpose of this article is to describe specific medical conditions that may worsen or present challenges to the athlete in a wilderness environment.

Danve, A., Reddy, A., Vakil-Gilani, K., Garg, N., Dinno, A., & Deodhar, A. (2015). Routine assessment of patient index data 3 score (RAPID3) correlates well with bath ankylosing spondylitis disease activity index (BASDAI) in the assessment of disease activity and monitoring progression of axial spondyloarthritis. *Clinical Rheumatology, 34*(1), 117-124.

Routine Assessment of Patient Index Data 3 (RAPID3) is a composite index, very useful for assessment of disease activity of various rheumatic diseases including RA. If RAPID3 can also reliably measure disease activity in axial spondyloarthritis (axSpA), it may prove to be a practical and effective quantitative assessment tool in busy practices. We studied the association of RAPID3 with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Patients with Ankylosing Spondylitis (AS) seen from 2007 to 2012 were classified as having AS or non-radiographic axial spondyloarthritis (nr-axSpA) using modified New York criteria and Assessment of SpondyloArthritis International Society criteria, respectively. Patients with simultaneous BASDAI and RAPID3 scores were enrolled (N = 112; 105 with AS, seven with nr-axSpA). Multiple regression and nonparametric receiver operating characteristics were used. Baseline mean (SD) BASDAI and RAPID3 were 4.2 (2.5) and 3.8 (2.3), respectively. Multiple linear regressions modeled a quadratic relationship between BASDAI and RAPID3 for 321 observations in 112 patients with axSpA (1) cross-sectionally: BASDAI predicted by RAPID3 (beta = 1.171; s.e. = 0.113, $p < 0.001$) and RAPID3(2) (beta = -0.037; s.e. = 0.014, $p = 0.011$) with an adjusted R (2) of 0.676; and (2) longitudinally: BASDAI predicted by RAPID3 (beta = 1.196; s.e. = 0.111, $p < 0.001$), RAPID3(2) (beta = -0.042; s.e. = 0.014, $p = 0.004$), and visit number (beta = -0.142; s.e. = 0.038, $p < 0.001$) with an adjusted R (2) of 0.689. RAPID3 (correctly classified) corresponded to BASDAI scores of 2, 4, and 6: 1.40 (85.8 %), 3.33 (81.9 %), and 5.43 (87.1 %), respectively. RAPID3 correlates well with BASDAI in monitoring axSpA patients (including AS) in cross-sectional and longitudinal follow-up. Since it also correlates with measures of disease activity of other rheumatic diseases including RA, RAPID3 could be an attractive measure for assessing and monitoring disease activity of several conditions seen in busy rheumatology practices.

Daroui, P., Jabbour, S. K., Herman, J. M., Abdel-Wahab, M., Azad, N., Blackstock, A. W., et al. (2015). ACR appropriateness criteria® resectable stomach cancer. *ONCOLOGY (United States), 29*(8)

Davare, M. A., Vellore, N. A., Wagner, J. P., Eide, C. A., Goodman, J. R., Drilon, A., et al. (2015). Structural insight into selectivity and resistance profiles of ROS1 tyrosine kinase inhibitors. *Proceedings of the National Academy of Sciences of the United States of America, 112*(39), E5381-90.

Oncogenic ROS1 fusion proteins are molecular drivers in multiple malignancies, including a subset of non-small cell lung cancer (NSCLC). The phylogenetic proximity of the ROS1 and anaplastic lymphoma kinase (ALK) catalytic domains led to the clinical repurposing of the Food and Drug Administration (FDA)-approved ALK inhibitor crizotinib as a ROS1 inhibitor. Despite the antitumor activity of crizotinib observed in both ROS1- and ALK-rearranged NSCLC patients, resistance due to acquisition of ROS1 or ALK kinase domain mutations has been observed clinically, spurring the development of second-generation inhibitors. Here, we profile the sensitivity and selectivity of seven ROS1 and/or ALK inhibitors at various levels of clinical development. In contrast to crizotinib's dual ROS1/ALK activity, cabozantinib (XL-184) and its structural analog foretinib (XL-880) demonstrate a striking selectivity for ROS1 over ALK. Molecular dynamics simulation studies reveal structural features that distinguish the ROS1 and ALK kinase domains and contribute to differences in binding site and kinase selectivity of the inhibitors tested. Cell-based resistance profiling studies demonstrate that the ROS1-selective inhibitors retain efficacy against the recently reported CD74-ROS1(G2032R) mutant whereas the dual ROS1/ALK inhibitors are ineffective. Taken together, inhibitor profiling and stringent characterization of the structure-function differences between the ROS1 and ALK kinase domains will facilitate future rational drug design for ROS1- and ALK-driven NSCLC and other malignancies.

Davis, M. M., Balasubramanian, B. A., Cifuentes, M., Hall, J., Gunn, R., Fernald, D., et al. (2015). Clinician staffing, scheduling, and engagement strategies among primary care practices delivering integrated care. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S32-40.

PURPOSE: To examine the interrelationship among behavioral health clinician (BHC) staffing, scheduling, and a primary care practice's approach to delivering integrated care. METHODS: Observational cross-case comparative analysis of 17 primary care practices in the United States focused on implementation of integrated care. Practices varied in size, ownership, geographic

location, and integrated care experience. A multidisciplinary team analyzed documents, practice surveys, field notes from observation visits, implementation diaries, and semistructured interviews using a grounded theory approach. RESULTS: Across the 17 practices, staffing ratios ranged from 1 BHC covering 0.3 to 36.5 primary care clinicians (PCCs). BHC scheduling varied from 50-minute prescheduled appointments to open, flexible schedules slotted in 15-minute increments. However, staffing and scheduling patterns generally clustered in 2 ways and enabled BHCs to be engaged by referral or warm handoff. Five practices predominantly used warm handoffs to engage BHCs and had higher BHC-to-PCC staffing ratios; multiple BHCs on staff; and shorter, more flexible BHC appointment schedules. Staffing and scheduling structures that enabled warm handoffs supported BHC engagement with patients concurrent with the identification of behavioral health needs. Twelve practices primarily used referrals to engage BHCs and had lower BHC-to-PCC staffing ratios and BHC schedules prefilled with visits. This enabled some BHCs to bill for services, but also made them less accessible to PCCs in when patients presented with behavioral health needs during a clinical encounter. Three of these practices were experimenting with open scheduling and briefer BHC visits to enable real-time access while managing resources. CONCLUSION: Practices' approaches to PCC-BHC staffing, scheduling, and delivery of integrated care mutually influenced each other and were shaped by the local context. Practice leaders, educators, clinicians, funders, researchers, and policy makers must consider these factors as they seek to optimize integrated systems of care.

De Lima, J. L. R., Soares, F. A., Remedios, A. C. S., Thom, G., Wirthlin, M., Aleixo, A., et al. (2015). A putative RA-like region in the brain of the scale-backed antbird, willisornis poecilinotus (furnariides, suboscines, passeriformes, thamnophilidae). *Genetics and Molecular Biology, 38*(3), 249-254.

De Michele, A., Yee, D., Berry, D. A., Albain, K. S., Benz, C. C., Boughey, J., et al. (2015). The neoadjuvant model is still the future for drug development in breast cancer. *Clinical Cancer Research, 21*(13), 2911-2915.

Deck, J., Guralnick, R., Walls, R., Blum, S., Haendel, M., Matsunaga, A., et al. (2015). Meeting report: Identifying practical applications of ontologies for biodiversity informatics. *Standards in Genomic Sciences, 10*(MAY2015)

Deffebach, M. E., & Humphrey, L. (2015). Lung cancer screening. *The Surgical Clinics of North America, 95*(5), 967-978.

Screening for lung cancer in high-risk individuals with annual low-dose computed tomography has been shown to reduce lung cancer mortality by 20% and is recommended by multiple health care organizations. Lung cancer screening is not a specific test; it is a process that involves appropriate selection of high-risk individuals, careful interpretation and follow-up of imaging, and annual testing. Screening should be performed in the context of a multidisciplinary program experienced in the diagnosis and management of lung nodules and early-stage lung cancer.

DeGruy, F. V., Ewigman, B., DeVoe, J. E., Hughes, L., James, P., Schneider, F. D., et al. (2015). A plan for useful and timely family medicine and primary care research. *Family Medicine, 47*(8), 636-642.

Delmar, J. A., Chou, T. H., Wright, C. C., Licon, M. H., Doh, J. K., Radhakrishnan, A., et al. (2015). Structural basis for the regulation of the MmpL transporters of mycobacterium tuberculosis. *The Journal of Biological Chemistry,*

The mycobacterial cell wall is critical to the virulence of these pathogens. Recent work shows that the mycobacterial membrane protein large (MmpL) family of transporters contributes to cell wall biosynthesis by exporting fatty acids and lipidic elements of the cell wall. The expression of the Mycobacterium tuberculosis MmpL proteins is controlled by a complex regulatory network, including the TetR-family transcriptional regulators Rv3249c and Rv1816. Here we report the crystal structures of these two regulators, revealing dimeric, two-domain molecules with architecture consistent with the TetR family of regulators. Buried extensively within the C-terminal regulatory domains of Rv3249c and Rv1816 we found fortuitous bound ligands, which were identified as palmitic acid (a fatty acid) and isopropyl laurate (a fatty acid ester), respectively. Our results suggest that fatty acids may be the natural ligands of these regulatory proteins. Using fluorescence polarization and electrophoretic mobility shift assays, we

demonstrate the recognition of promoter and intragenic regions of multiple mmpL genes by these proteins. Binding of palmitic acid renders these regulators incapable of interacting with their respective operator DNAs, which will result in derepression of the corresponding mmpL genes. Taken together, these experiments provide new perspectives on the regulation of the MmpL family of transporters.

DeVoe, J. E., Tillotson, C. J., Angier, H., & Wallace, L. S. (2015). Predictors of Children's health insurance coverage discontinuity in 1998 versus 2009: Parental coverage continuity plays a major role. *Maternal and Child Health Journal, 19*(4), 889-896.

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., et al. (2015). Report of the NIH task force on research standards for chronic low back pain. *International Journal of Therapeutic Massage & Bodywork, 8*(3), 16-33.

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. The NIH Pain Consortium therefore charged a Research Task Force (RTF) to draft standards for research on cLBP. The resulting multidisciplinary panel recommended using 2 questions to define cLBP; classifying cLBP by its impact (defined by pain intensity, pain interference, and physical function); use of a minimal data set to describe research participants (drawing heavily on the PROMIS methodology); reporting "responder analyses" in addition to mean outcome scores; and suggestions for future research and dissemination. The Pain Consortium has approved the recommendations, which investigators should incorporate into NIH grant proposals. The RTF believes these recommendations will advance the field, help to resolve controversies, and facilitate future research addressing the genomic, neurologic, and other mechanistic substrates of chronic low back pain. We expect 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 minimal dataset, reporting outcomes, and future research. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes.

Dieckmann, N. F., Johnson, B. B., Gregory, R., Mayorga, M., Han, P. K., & Slovic, P. (2015). Public perceptions of expert disagreement: Bias and incompetence or a complex and random world? *Public Understanding of Science (Bristol, England),*

Expert disputes can present laypeople with several challenges including trying to understand why such disputes occur. In an online survey of the US public, we used a psychometric approach to elicit perceptions of expert disputes for 56 forecasts sampled from seven domains. People with low education, or with low self-reported topic knowledge, were most likely to attribute disputes to expert incompetence. People with higher self-reported knowledge tended to attribute disputes to expert bias due to financial or ideological reasons. The more highly educated and cognitively able were most likely to attribute disputes to natural factors, such as the irreducible complexity and randomness of the phenomenon. Our results show that laypeople tend to use coherent-albeit potentially overly narrow-attributions to make sense of expert disputes and that these explanations vary across different segments of the population. We highlight several important implications for scientists, risk managers, and decision makers.

Dobbe, R., Chang, Y. -., Korkola, J., Gray, J., & Tomlin, C. (2015). Heterogeneity in cancer dynamics: A convex formulation to dissect dynamic trajectories and infer LTV models of networked systems. *Proceedings of the American Control Conference, , 2015-July.* pp. 4398-4403.

Dobscha, S. K., Denneson, L. M., Jacobson, L. E., Williams, H. B., Cromer, R., & Woods, S. (2015). VA mental health clinician experiences and attitudes toward OpenNotes. *General Hospital Psychiatry,* OBJECTIVE: To describe Department of Veterans Affairs (VA) mental health clinician attitudes toward and experiences with OpenNotes (also known as Blue Button), which provides patients direct access to clinical notes online. METHOD: A 35-item online survey was administered to 263 mental health clinicians and nurses from one VA Medical Center. RESULTS: Seventy-nine percent of eligible subjects participated. Most respondents agreed or somewhat agreed that OpenNotes is a good idea in general, but only half agreed that making mental health notes available online is a

good idea. Most believed that patients will better remember plans of care and be better prepared for visits. Most also felt that patients will worry more and request changes in notes. Many clinicians reported being less detailed and changing the tone of their notes. CONCLUSION: As a group, mental health clinicians are positive about OpenNotes in general but ambivalent about the use of OpenNotes in mental health care. The results call for research on outcomes of OpenNotes use in mental health and to develop education and support to help clinicians adapt to OpenNotes.

Docherty, A., & Dieckmann, N. (2015). Is there evidence of failing to fail in our schools of nursing? *Nursing Education Perspectives, 36*(4), 226-231.

Dodge, H. H., Zhu, J., Mattek, N. C., Austin, D., Kornfeld, J., & Kaye, J. A. (2015). Use of high-frequency in-home monitoring data may reduce sample sizes needed in clinical trials. *PloS One, 10*(9), e0138095.

BACKGROUND: Trials in Alzheimer's disease are increasingly focusing on prevention in asymptomatic individuals. This poses a challenge in examining treatment effects since currently available approaches are often unable to detect cognitive and functional changes among asymptomatic individuals. Resultant small effect sizes require large sample sizes using biomarkers or secondary measures for randomized controlled trials (RCTs). Better assessment approaches and outcomes capable of capturing subtle changes during asymptomatic disease stages are needed. OBJECTIVE: We aimed to develop a new approach to track changes in functional outcomes by using individual-specific distributions (as opposed to group-norms) of unobtrusive continuously monitored in-home data. Our objective was to compare sample sizes required to achieve sufficient power to detect prevention trial effects in trajectories of outcomes in two scenarios: (1) annually assessed neuropsychological test scores (a conventional approach), and (2) the likelihood of having subject-specific low performance thresholds, both modeled as a function of time. METHODS: One hundred nineteen cognitively intact subjects were enrolled and followed over 3 years in the Intelligent Systems for Assessing Aging Change (ISAAC) study. Using the difference in empirically identified time slopes between those who remained cognitively intact during follow-up (normal control, NC) and those who transitioned to mild cognitive impairment (MCI), we estimated comparative sample sizes required to achieve up to

80% statistical power over a range of effect sizes for detecting reductions in the difference in time slopes between NC and MCI incidence before transition. RESULTS: Sample size estimates indicated approximately 2000 subjects with a follow-up duration of 4 years would be needed to achieve a 30% effect size when the outcome is an annually assessed memory test score. When the outcome is likelihood of low walking speed defined using the individual-specific distributions of walking speed collected at baseline, 262 subjects are required. Similarly for computer use, 26 subjects are required. CONCLUSIONS: Individual-specific thresholds of low functional performance based on high-frequency in-home monitoring data distinguish trajectories of MCI from NC and could substantially reduce sample sizes needed in dementia prevention RCTs.

Drerup, C. M., & Nechiporuk, A. V. (2015). *In vivo analysis of axonal transport in zebrafish*

D'Souza, A., Dispenzieri, A., Wirk, B., Zhang, M. J., Huang, J., Gertz, M. A., et al. (2015). Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: A center for international blood and marrow transplant research study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology,*

PURPOSE: Autologous hematopoietic cell transplantation, or autotransplantation, is effective in light-chain amyloidosis (AL), but it is associated with a high risk of early mortality (EM). In a multicenter randomized comparison against oral chemotherapy, autotransplantation was associated with 24% EM. We analyzed trends in outcomes after autologous hematopoietic cell transplantation for AL in North America. PATIENTS AND METHODS: Between 1995 and 2012, 1,536 patients with AL who underwent autotransplantation at 134 centers were identified in the Center for International Blood and Marrow Transplant Research database. EM and overall survival (OS) were analyzed in three time cohorts: 1995 to 2000 (n = 140), 2001 to 2006 (n = 596), and 2007 to 2012 (n = 800). Hematologic and renal responses and factors associated with EM, relapse and/or progression, progression-free survival and OS were analyzed in more recent subgroups from 2001 to 2006 (n = 197) and from 2007 to 2012 (n = 157). RESULTS: Mortality at 30 and 100 days progressively declined over successive time periods from 11% and 20%, respectively, in 1995 to 2000 to 5% and 11%, respectively, in 2001 to 2006, and to 3% and 5%, respectively, in 2007 to 2012. Correspondingly, 5-year OS improved from 55% in 1995 to 2000

to 61% in 2001 to 2006 and to 77% in 2007 to 2012. Hematologic response to transplantation improved in the latest cohort. Renal response rate was 32%. Centers performing more than four AL transplantations per year had superior survival outcomes. In the multivariable analysis, cardiac AL was associated with high EM and inferior progression-free survival and OS. Autotransplantation in 2007 to 2012 and use of higher dosages of melphalan were associated with a lowered relapse risk. A Karnofsky score less than 80 and creatinine levels 2 mg/m2 or greater were associated with worsened OS. CONCLUSION: Post-transplantation survival in AL has improved, with a dramatic reduction in early post-transplantation mortality and excellent 5-year survival. The risk-benefit ratio for autotransplantation has changed, and randomized comparison with nontransplantation approaches is again warranted.

Du, J., Lu, W., Wu, S., Cheng, Y., & Gouaux, E. (2015). Glycine receptor mechanism elucidated by electron cryo-microscopy. *Nature,*

The strychnine-sensitive glycine receptor (GlyR) mediates inhibitory synaptic transmission in the spinal cord and brainstem and is linked to neurological disorders, including autism and hyperekplexia. Understanding of molecular mechanisms and pharmacology of glycine receptors has been hindered by a lack of high-resolution structures. Here we report electron cryo-microscopy structures of the zebrafish alpha1 GlyR with strychnine, glycine, or glycine and ivermectin (glycine/ivermectin). Strychnine arrests the receptor in an antagonist-bound closed ion channel state, glycine stabilizes the receptor in an agonist-bound open channel state, and the glycine/ivermectin complex adopts a potentially desensitized or partially open state. Relative to the glycine-bound state, strychnine expands the agonist-binding pocket via outward movement of the C loop, promotes rearrangement of the extracellular and transmembrane domain 'wrist' interface, and leads to rotation of the transmembrane domain towards the pore axis, occluding the ion conduction pathway. These structures illuminate the GlyR mechanism and define a rubric to interpret structures of Cys-loop receptors.

Eden, K. B., Scariati, P., Klein, K., Watson, L., Remiker, M., Hribar, M., et al. (2015). Mammography decision aid reduces decisional conflict for women in their forties considering screening. *Journal of Women's Health (2002),*

BACKGROUND: Clinical guidelines recommend a personalized approach to mammography screening for women in their forties; however, methods to do so are lacking. An evidence-based mammography screening decision aid was developed as an electronic mobile application and evaluated in a before-after study. METHODS: The decision aid (Mammopad) included modules on breast cancer, mammography, risk assessment, and priority setting about screening. Women aged 40-49 years who were patients of rural primary care clinics, had no major risk factors for breast cancer, and no mammography during the previous year were invited to use the decision aid. Twenty women participated in pretesting of the decision aid and 75 additional women completed the before-after study. The primary outcome was decisional conflict measured before and after using Mammopad. Secondary outcomes included decision self-efficacy and intention to begin or continue mammography screening. Differences comparing measures before versus after use were determined using Wilcoxon signed rank tests. RESULTS: After using Mammopad, women reported reduced decisional conflict based on mean Decisional Conflict Scale scores overall (46.33 versus 8.33; $Z = -7.225$; $p < 0.001$) and on all subscales ($p < 0.001$). Women also reported increased mean Decision Self-Efficacy Scale scores (79.67 versus 95.73; $Z = 6.816$, $p < 0.001$). Although 19% of women changed their screening intentions, this was not statistically significant. CONCLUSIONS: Women reported less conflict about their decisions for mammography screening, and felt more confident to make decisions after using Mammopad. This approach may help guide women through the decision making process to determine personalized screening choices that are appropriate for them.

Elsea, C. R., Kneiss, J. A., & Wood, L. J. (2015). Induction of IL-6 by cytotoxic chemotherapy is associated with loss of lean body and fat mass in tumor-free female mice. *Biological Research for Nursing, 17*(5), 549-557.

Emens, J. S., & Burgess, H. J. (2015). Effect of light and melatonin and other melatonin receptor agonists on human circadian physiology. *Sleep Medicine Clinics,*

Engeland, C. G., Hugo, F. N., Hilgert, J. B., Nascimento, G. G., Junges, R., Lim, H. J., et al. (2015). The effects of psychological distress on salivary secretory immunity. *Brain, Behavior, and Immunity,*

Stress-induced impairments of mucosal immunity may increase susceptibility to infectious diseases. The present study investigated the association of perceived stress, depressive symptoms, and loneliness with salivary levels of secretory immunoglobulin A (S-IgA), the subclasses S-IgA1, S-IgA2, and their transporter molecule Secretory Component (SC). S-IgA/SC, IgA1/SC and IgA2/SC ratios were calculated to assess the differential effects of stress on immunoglobulin transport versus availability. This study involved 113 university students, in part selected on high scores on the UCLA Loneliness Scale and/or the Beck Depression Inventory. Stress levels were assessed using the Perceived Stress Scale. Unstimulated saliva was collected and analyzed for total S-IgA and its subclasses, as well as SC and total salivary protein. Multiple linear regression analyses, adjusted for gender, age, health behaviors, and concentration effects (total protein) revealed that higher perceived stress was associated with lower levels of IgA1 but not IgA2. Perceived stress, loneliness and depressive symptoms were all associated with lower IgA1/SC ratios. Surprisingly, higher SC levels were associated with loneliness and depressive symptoms, indicative of enhanced transport activity, which explained a lower IgA1/SC ratio (loneliness and depression) and IgA2/SC ratio (depression). This is the first study to investigate the effects of protracted psychological stress across S-IgA subclasses and its transporter SC. Psychological stress was negatively associated with secretory immunity, specifically IgA1. The lower immunoglobulin/transporter ratio that was associated with higher loneliness and depression suggested a relative immunoglobulin depletion, whereby availability was not keeping up with enhanced transport demand.

Ewing, R., Tian, G., Goates, J. P., Zhang, M., Greenwald, M. J., Joyce, A., et al. (2015). Varying influences of the built environment on household travel in 15 diverse regions of the united states. *Urban Studies, 52*(13), 2330-2348.

Fagnan, L. J., Michaels, L., Ramsey, K., Shearer, S., Droppers, O., & Gallia, C. (2015). Rural clinician evaluation of children's health care quality measures: An oregon rural practice-based research network (ORPRN) study. *Journal of the American Board of Family Medicine : JABFM, 28*(5), 595-604.

BACKGROUND: Responding to quality metrics is an accepted and expected component of the

current health care environment. Little is known about which measures physicians identify as a priority when reporting the quality of care to their patients, especially the care of children in rural settings. The objective of this study is for physicians caring for children in rural communities to identify which of the initial core sets of 24 child health quality measures are useful and are a priority for reporting and improving care. METHODS: A survey was sent to rural Oregon physicians who provide care to children. RESULTS: Of 955 eligible physicians, 172 (18%) completed the survey. The majority of respondents were family physicians (84%), and most respondents (58%) were in private practice. The child health measures stratified into 3 priority tiers: high, medium, and low priority. The top-tier priority measures included childhood immunization status, well-child visits, adolescent immunization status, body mass index assessment, and developmental screening. Dental treatment services, adequate prenatal care, and lower-birth-weight infants were among the lower-tier measures. CONCLUSIONS: The priority measures identified by rural family physicians reflect the relevance of the selected measures to their daily practice responsibilities, with missed opportunities to improve community health.

Fan, D., Chen, S., Johnson, R. L., & Tratnyek, P. G. (2015). Field deployable chemical redox probe for quantitative characterization of carboxymethylcellulose modified nano zerovalent iron. *Environmental Science and Technology, 49*(17), 10589-10597.

Feng, S., Gale, M. J., Fay, J. D., Faridi, A., Titus, H. E., Garg, A. K., et al. (2015). Assessment of different sampling methods for measuring and representing macular cone density using flood-illuminated adaptive optics. *Investigative Ophthalmology and Visual Science, 56*(10), 5751-5763.

Firth, C. L., Sazie, E., Hedberg, K., Drach, L., & Maher, J. (2015). Female inmates with diabetes: Results from changes in a prison food environment. *Women's Health Issues,*

Fischer, S., Lin, D., Simon, R. M., Howard, L., Aronson, W. J., Terris, M. K., et al. (2015). Pathologic gleason 8-10: Do all men do poorly? results from the search database. *BJU International,* OBJECTIVE: To determine whether there are subsets of men with pathologic high-grade disease (Gleason 8-10) who have particularly high or low 2-year BCR risk after radical prostatectomy (RP) when stratified into groups based on combinations of pathologic features such as surgical

margins (SM), extracapsular extension (ECE) and seminal vesicle invasion (SVI). METHODS: We identified 459 patients treated with RP with pathologic Gleason 8-10 in the SEARCH database. Patients were stratified into 5 groups based on pathological characteristics - Group 1: men with negative surgical margins and no extracapsular extension (-SM/-ECE), Group 2 (+SM/-ECE), Group 3 (-SM/+ECE), Group 4 (+SM/+ECE), and Group 5: men with SVI (+SVI). Cox proportional hazards models and the log-rank test were used to compare BCR among the groups. RESULTS: At 2-years post-RP, pathological group was significantly correlated with BCR (log-rank, $p<0.001$) with patients in Group 5 (+SVI) having the highest BCR risk (66%) and Group 1 (-SM/-ECE) having the lowest risk (14%). When we compared groups 2, 3, and 4, to each other, there was no significant difference in BCR among the groups (~50% 2-year BCR risk, log-rank, $p=0.28$). Results were similar when adjusting for PSA, age, pathological Gleason sum, and clinical stage or after excluding men who received adjuvant therapy. CONCLUSION: In patients with high grade (Gleason 8-10) prostate cancer after RP, the presence of either positive SM, ECE, or SVI are all associated with an increased risk of early BCR with 2-year BCR risk of 50% or higher. On the contrary, men with organ-confined margin-negative disease have a very low risk of early BCR despite Gleason 8-10 disease.

Fleseriu, M., & Petersenn, S. (2015). Medical therapy for Cushing's disease: Adrenal steroidogenesis inhibitors and glucocorticoid receptor blockers. *Pituitary, 18*(2), 245-252.

Flickinger, T. E., Saha, S., Roter, D., Korthuis, P. T., Sharp, V., Cohn, J., et al. (2015). Clinician empathy is associated with differences in patient-clinician communication behaviors and higher medication self-efficacy in HIV care. *Patient Education and Counseling,*
OBJECTIVE: We examined associations of clinicians' empathy with patient-clinician communication behaviors, patients' rating of care, and medication self-efficacy. METHODS: We analyzed 435 adult patients and 45 clinicians at four outpatient HIV care sites in the United States. Negative binomial regressions investigated associations between clinician empathy and patient-clinician communication, assessed using the Roter Interaction Analysis System (RIAS). Logistic regressions investigated associations between clinician empathy and patient ratings of

clinician communication, overall satisfaction, and medication self-efficacy. RESULTS: Clinicians in the highest vs. lowest empathy tertile engaged in less explicitly emotional talk (IRR 0.79, p<0.05), while clinicians in the middle vs. lowest engaged in more positive talk (IRR 1.31, p<0.05), more questions (IRR 1.42, p<0.05), and more patient activating talk (IRR 1.43, p<0.05). Patients of higher empathy clinicians disclosed more psychosocial and biomedical information. Patients of clinicians in both the middle and highest (vs. lowest) empathy tertiles had greater odds of reporting highest medication self-efficacy (OR 1.80, 95% CI 1.16-2.80; OR 2.13, 95% CI 1.37-3.32). CONCLUSIONS: Clinician empathy may be expressed through addressing patient engagement in care, by fostering cognitive, rather than primarily emotional, processing. PRACTICE IMPLICATIONS: Clinicians should consider enhancing their own empathic capacity, which may encourage patients' self-efficacy in medication adherence.

Flickinger, T. E., Saha, S., Roter, D., Korthuis, P. T., Sharp, V., Cohn, J., et al. (2015). Respecting patients is associated with more patient-centered communication behaviors in clinical encounters. *Patient Education and Counseling,*

OBJECTIVE: Attitudes towards patients may influence how clinicians interact. We investigated whether respect for patients was associated with communication behaviors during HIV care encounters. METHODS: We analyzed audio-recordings of visits between 413 adult HIV-infected patients and 45 primary HIV care providers. The independent variable was clinician-reported respect for the patient and outcomes were clinician and patient communication behaviors assessed by the Roter Interaction Analysis System (RIAS). We performed negative binomial regressions for counts outcomes and linear regressions for global outcomes. RESULTS: When clinicians had higher respect for a patient, they engaged in more rapport-building, social chitchat, and positive talk. Patients of clinicians with higher respect for them engaged in more rapport-building, social chitchat, positive talk, and gave more psychosocial information. Encounters between patients and clinicians with higher respect for them had more positive clinician emotional tone [regression coefficient 2.97 (1.92-4.59)], more positive patient emotional tone [2.71 (1.75-4.21)], less clinician verbal dominance [0.81 (0.68-0.96)] and more patient-centeredness [1.28 (1.09-1.51)]. CONCLUSIONS: Respect is associated with positive and patient-centered communication behaviors during encounters. PRACTICE IMPLICATIONS: Clinicians

should be mindful of their respectful attitudes and work to foster positive regard for patients. Educators should consider methods to enhance trainees' respect in communication skills training.

Flowers, C. R., Brown, J. R., Rosenthal, H., Stock, W., Katzen, H. I., Cohen, J. B., et al. (2015). A phase 2 trial of fludarabine combined with subcutaneous alemtuzumab for the treatment of Relapsed/Refractory B-cell chronic lymphocytic leukemia. *Clinical Lymphoma, Myeloma & Leukemia,*

BACKGROUND: Alemtuzumab is effective in fludarabine-refractory patients with chronic lymphocytic leukemia. We performed a phase 2 study of alemtuzumab in combination with fludarabine in patients with relapsed disease. PATIENTS AND METHODS: Patients received alemtuzumab and fludarabine daily on days 1 to 5 of a 28-day cycle for up to 6 cycles with the primary objective of determining the rate of complete response. Of 60 enrolled patients, 51 had previously received fludarabine, and 60% had received 3 or more prior therapies. RESULTS: Five patients experienced complete response (8.3%) and 12 experienced partial response, yielding an overall response rate of 28.3% for the intention-to-treat population. Among the 41 patients who completed at least 4 cycles of therapy, the complete response rate was 20%. Median progression-free survival was 211 days. Forty-seven percent of patients experienced cytomegalovirus viremia, including 4 patients with symptomatic cytomegalovirus disease. All patients responded to antiviral therapy. CONCLUSION: Despite some evidence of efficacy in this setting, the primary end point for the study was not met. In the era of targeted agents that are well tolerated, the combination of fludarabine and alemtuzumab should be used rarely for a select group of fit patients who are refractory to standard therapies.

Fried-Oken, M., Mooney, A., & Peters, B. (2015). Supporting communication for patients with neurodegenerative disease. *Neurorehabilitation, 37*(1), 69-87.

Gao, L., Bin, L., Rafaels, N. M., Huang, L., Potee, J., Ruczinski, I., et al. (2015). Targeted deep sequencing identifies rare loss-of-function variants in IFNGR1 for risk of atopic dermatitis complicated by eczema herpeticum. *The Journal of Allergy and Clinical Immunology,*

BACKGROUND: A subset of atopic dermatitis is associated with increased susceptibility to eczema herpeticum (ADEH+). We previously reported that common single nucleotide polymorphisms

(SNPs) in the IFN-gamma (IFNG) and IFN-gamma receptor 1 (IFNGR1) genes were associated with the ADEH+ phenotype. OBJECTIVE: We sought to interrogate the role of rare variants in interferon pathway genes for the risk of ADEH+. METHODS: We performed targeted sequencing of interferon pathway genes (IFNG, IFNGR1, IFNAR1, and IL12RB1) in 228 European American patients with AD selected according to their eczema herpeticum status, and severity was measured by using the Eczema Area and Severity Index. Replication genotyping was performed in independent samples of 219 European American and 333 African American subjects. Functional investigation of loss-of-function variants was conducted by using site-directed mutagenesis. RESULTS: We identified 494 single nucleotide variants encompassing 105 kb of sequence, including 145 common, 349 (70.6%) rare (minor allele frequency <5%), and 86 (17.4%) novel variants, of which 2.8% were coding synonymous, 93.3% were noncoding (64.6% intronic), and 3.8% were missense. We identified 6 rare IFNGR1 missense variants, including 3 damaging variants (Val14Met [V14M], Val61Ile, and Tyr397Cys [Y397C]) conferring a higher risk for ADEH+ (P = .031). Variants V14M and Y397C were confirmed to be deleterious, leading to partial IFNGR1 deficiency. Seven common IFNGR1 SNPs, along with common protective haplotypes (2-7 SNPs), conferred a reduced risk of ADEH+ (P = .015-.002 and P = .0015-.0004, respectively), and both SNP and haplotype associations were replicated in an independent African American sample (P = .004-.0001 and P = .001-.0001, respectively). CONCLUSION: Our results provide evidence that both genetic variants in the gene encoding IFNGR1 are implicated in susceptibility to the ADEH+ phenotype.

Gao, L., Bin, L., Rafaels, N. M., Huang, L., Potee, J., Ruczinski, I., et al. (2014). Targeted deep sequencing identifies rare loss-of-function variants in IFNGR1 for risk of atopic dermatitis complicated by eczema herpeticum. *Journal of Allergy and Clinical Immunology,*

Gartlehner, G., Dobrescu, A., Evans, T. S., Bann, C., Robinson, K. A., Reston, J., et al. (2015). TEMPORARY REMOVAL: The predictive validity of quality of evidence grades for the stability of effect estimates was low: A meta-epidemiological study. *Journal of Clinical Epidemiology,*
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Giunzioni, I., & Tavori, H. (2015). New developments in atherosclerosis: Clinical potential of PCSK9 inhibition. *Vascular Health and Risk Management, 11*, 493-501.

Pro-protein convertase subtilisin/kexin type 9 (PCSK9) is a secreted 692-amino acid protein that binds surface low-density lipoprotein (LDL) receptor (LDLR) and targets it toward lysosomal degradation. As a consequence, the number of LDLRs at the cell surface is decreased, and LDL-cholesterol (LDL-C) clearance is reduced, a phenomenon that is magnified by gain-of-function mutations of PCSK9. In contrast, loss-of-function mutations of PCSK9 result in increased surface LDLR and improved LDL-C clearance. This provides the rationale for targeting PCSK9 in hypercholesterolemic subjects as a means to lower LDL-C levels. Monoclonal antibodies (mAbs) against PCSK9 that block its interaction with the LDLR have been developed in the past decade. Two companies have recently received the approval for their anti-PCSK9 mAbs by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) Regeneron/Sanofi, with alirocumab (commercial name - PRALUENT((R))) and, Amgen with evolocumab (commercial name - Repatha). The introduction of anti-PCSK9 mAbs will provide an alternative therapeutic strategy to address many of the unmet needs of current lipid-lowering therapies, such as inability to achieve goal LDL-C level, or intolerance and aversion to statins. This review will focus on the kinetics of PCSK9, pharmacokinetics and pharmacodynamics of anti-PCSK9 mAbs, and recent data linking PCSK9 and anti-PCSK9 mAbs to cardiovascular events. Moreover, it will highlight the unanswered questions that still need to be addressed in order to understand the physiologic function, kinetics, and dynamics of PCSK9.

Giunzioni, I., Tavori, H., Covarrubias, R., Major, A. S., Ding, L., Zhang, Y., et al. (2015). Local effects of human PCSK9 on the atherosclerotic lesion. *The Journal of Pathology,*

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) promotes atherosclerosis by increasing low-density lipoprotein (LDL) cholesterol levels through degradation of hepatic LDL receptors (LDLR). Studies have described the systemic effects of PCSK9 on atherosclerosis, but whether PCSK9 has local and direct effects on the plaque in unknown. To study the local effect of human

PCSK9 (hPCSK9) on atherosclerotic lesion composition independently of changes in serum cholesterol levels we generated chimeric mice expressing hPCSK9 exclusively from macrophages using marrow from hPCSK9 transgenic (hPCSK9tg) mice transplanted into apoE-/- and LDLR-/- mice, which were then placed on a high fat diet for 8 wk. We further characterized the effect of hPCSK9 expression on the inflammatory responses in the spleen and by mouse peritoneal macrophages (MPM) in vitro. We found that MPM from transgenic mice express both murine (m) Pcsk9 and hPCSK9 and that the latter reduces macrophage LDLR and LRP1 surface levels. hPCSK9 was detected in serum of mice transplanted with hPCSK9tg marrow, but did not influence lipid levels or atherosclerotic lesion size. However, marrow-derived PCSK9 progressively accumulated in lesions of apoE-/- recipient mice while increasing the infiltration of Ly6Chi inflammatory monocytes by 32% compared with controls. Expression of hPCSK9 also increased CD11b and Ly6Chi positive cell numbers in spleens of apoE-/- mice. In vitro, expression of hPCSK9 in LPS-stimulated macrophages increased mRNA levels of the pro-inflammatory markers Tnf and Il1b (40% and 45%, respectively) and suppressed those of the anti-inflammatory markers Il10 and Arg1 (30% and 44%, respectively). All PCSK9 effects were LDLR-dependent as PCSK9 protein was not detected in lesions of LDLR-/- recipient mice and did not affect macrophage or splenocyte inflammation. In conclusion, PCSK9 directly increases atherosclerotic lesion inflammation in an LDLR-dependent but cholesterol-independent mechanism, suggesting that therapeutic PCSK9 inhibition may have vascular benefits secondary to LDL reduction.

Glynn, J. J., Jones, C. M., Anderson, D. E., Pavcnik, D., & Hinds, M. T. (2015). In vivo assessment of two endothelialization approaches on bioprosthetic valves for the treatment of chronic deep venous insufficiency. *Journal of Biomedical Materials Research.Part B, Applied Biomaterials,* Chronic deep venous insufficiency is a debilitating disease with limited therapeutic interventions. A bioprosthetic venous valve could not only replace a diseased valve, but has the potential to fully integrate into the patient with a minimally invasive procedure. Previous work with valves constructed from small intestinal submucosa (SIS) showed improvements in patients' symptoms in clinical studies; however, substantial thickening of the implanted valve leaflets also occurred. As endothelial cells are key regulators of vascular homeostasis, their presence on the SIS valves may reduce the observed thickening. This work tested an off-the-shelf approach to capture

circulating endothelial cells in vivo using biotinylated antikinase insert domain receptor antibodies in a suspended leaflet ovine model. The antibodies on SIS were oriented to promote cell capture and showed positive binding to endothelial cells in vitro; however, no differences were observed in leaflet thickness in vivo between antibody-modified and unmodified SIS. In an alternative approach, valves were pre-seeded with autologous endothelial cells and tested in vivo. Nearly all the implanted pre-seeded valves were patent and functioning; however, no statistical difference was observed in valve thickness with cell pre-seeding. Additional cell capture schemes or surface modifications should be examined to find an optimal method for encouraging SIS valve endothelialization to improve long-term valve function in vivo. (c) 2015 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2015.

Goenezen, S., Chivukula, V. K., Midgett, M., Phan, L., & Rugonyi, S. (2015). 4D subject-specific inverse modeling of the chick embryonic heart outflow tract hemodynamics. *Biomechanics and Modeling in Mechanobiology,*

Blood flow plays a critical role in regulating embryonic cardiac growth and development, with altered flow leading to congenital heart disease. Progress in the field, however, is hindered by a lack of quantification of hemodynamic conditions in the developing heart. In this study, we present a methodology to quantify blood flow dynamics in the embryonic heart using subject-specific computational fluid dynamics (CFD) models. While the methodology is general, we focused on a model of the chick embryonic heart outflow tract (OFT), which distally connects the heart to the arterial system, and is the region of origin of many congenital cardiac defects. Using structural and Doppler velocity data collected from optical coherence tomography, we generated 4D ([Formula: see text]) embryo-specific CFD models of the heart OFT. To replicate the blood flow dynamics over time during the cardiac cycle, we developed an iterative inverse-method optimization algorithm, which determines the CFD model boundary conditions such that differences between computed velocities and measured velocities at one point within the OFT lumen are minimized. Results from our developed CFD model agree with previously measured hemodynamics in the OFT. Further, computed velocities and measured velocities differ by [Formula: see text]15 % at locations that were not used in the optimization, validating the model. The presented methodology can be used in quantifications of embryonic cardiac

hemodynamics under normal and altered blood flow conditions, enabling an in-depth quantitative study of how blood flow influences cardiac development.

Gold, R., Burdick, T., Angier, H., Wallace, L., Nelson, C., Likumahuwa-Ackman, S., et al. (2015). Improve synergy between health information exchange and electronic health records to increase rates of continuously insured patients. *EGEMS (Washington, DC), 3*(1), 1158-9214.1158. eCollection 2015.

INTRODUCTION: The Affordable Care Act increases health insurance options, yet many Americans may struggle to consistently maintain coverage. While health care providers have traditionally not been involved in providing insurance enrollment support to their patients, the ability for them to do so now exists. We propose that providers could capitalize on the expansion of electronic health records (EHRs) and the advances in health information exchanges (HIEs) to improve their patients' insurance coverage rates and continuity. EVIDENCE FOR ARGUMENT: We describe a project in which we are building strategies for linking, and thus improving synergy between, payer and EHR data. Through this effort, care teams will have access to new automated tools and increased EHR functionality designed to help them assist their patients in obtaining and maintaining health insurance coverage. SUGGESTION FOR THE FUTURE: The convergence of increasing EHR adoption, improving HIE functionality, and expanding insurance coverage options, creates new opportunities for clinics to help their patients obtain public health insurance. Harnessing this nascent ability to exchange information between payers and providers may improve synergies between HIE and EHRs, and thus support clinic-based efforts to keep patients continuously insured.

Goldenberg, N. A., Abshire, T., Blatchford, P. J., Fenton, L. Z., Halperin, J. L., Hiatt, W. R., et al. (2015). Multicenter randomized controlled trial on duration of therapy for thrombosis in children and young adults (the kids-DOTT trial): Pilot/feasibility phase findings. *Journal of Thrombosis and Haemostasis, 13*(9), 1597-1605.

Gordon, N., Skinner, A. M., Pommier, R. F., Schillace, R. V., O'Neill, S., Peckham, J. L., et al. (2015). Gene expression signatures of breast cancer stem and progenitor cells do not exhibit features of warburg metabolism. *Stem Cell Research & Therapy, 6*(1), 157-015-0153-7.

INTRODUCTION: Cancers are believed to adapt to continual changes in glucose and oxygen availability by relying almost exclusively on glycolytic metabolism for energy (i.e. the Warburg effect). The process by which breast cancers sustain growth in avascular tissue is thought to be mediated via aberrant hypoxia response with ensuing shifts in glycolytic metabolism. Given their role in initiating and perpetuating tumors, we sought to determine whether breast cancer stem and progenitor cells play an instrumental role in this adaptive metabolic response. METHODS: Breast cancer stem/progenitor cells were isolated from invasive ductal carcinomas, and benign stem cells (SC) were isolated from reduction mammoplasty tissues. Relative expression of 33 genes involved in hypoxia and glucose metabolism was evaluated in flow cytometrically isolated stem and progenitor cell populations. Significance between cohorts and cell populations was determined using Student's 2-tailed t test. RESULTS: While benign stem/progenitor cells exhibited few significant inter-group differences in expression of genes involved in hypoxia regulation or glucose metabolism, breast cancer stem/progenitor cells demonstrated significant inter-group variability. Breast cancer stem/progenitor cells adapted to microenvironments through changes in stem cell numbers and transcription of glycolytic genes. One of four breast cancer stem/progenitor cells subpopulations exhibited an aerobic glycolysis gene expression signature. This subpopulation comprises the majority of the tumor and therefore best reflects invasive ductal carcinoma tumor biology. Although PI3K/AKT mutations are associated with increased proliferation of breast cancer cells, mutations in breast cancer stem/progenitor cells subpopulations did not correlate with changes in metabolic gene expression. CONCLUSIONS: The adaptive capacity of breast cancer stem/progenitor cells may enable tumors to survive variable conditions encountered during progressive stages of cancer growth.

Grahl, N., Demers, E. G., Lindsay, A. K., Harty, C. E., Willger, S. D., Piispanen, A. E., et al. (2015). Mitochondrial activity and Cyr1 are key regulators of Ras1 activation of C. albicans virulence pathways. *PLoS Pathogens, 11*(8)

Guizzetti, M. (2015). *Fetal alcohol spectrum disorders: Effects and mechanisms of ethanol on the developing brain*

Gunn, R., Davis, M. M., Hall, J., Heintzman, J., Muench, J., Smeds, B., et al. (2015). Designing clinical space for the delivery of integrated behavioral health and primary care. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S52-62.

PURPOSE: This study sought to describe features of the physical space in which practices integrating primary care and behavioral health care work and to identify the arrangements that enable integration of care. METHODS: We conducted an observational study of 19 diverse practices located across the United States. Practice-level data included field notes from 2-4-day site visits, transcripts from semistructured interviews with clinicians and clinical staff, online implementation diary posts, and facility photographs. A multidisciplinary team used a 4-stage, systematic approach to analyze data and identify how physical layout enabled the work of integrated care teams. RESULTS: Two dominant spatial layouts emerged across practices: type-1 layouts were characterized by having primary care clinicians (PCCs) and behavioral health clinicians (BHCs) located in separate work areas, and type-2 layouts had BHCs and PCCs sharing work space. We describe these layouts and the influence they have on situational awareness, interprofessional "bumpability," and opportunities for on-the-fly communication. We observed BHCs and PCCs engaging in more face-to-face methods for coordinating integrated care for patients in type 2 layouts (41.5% of observed encounters vs 11.7%; P < .05). We show that practices needed to strike a balance between professional proximity and private work areas to accomplish job tasks. Private workspace was needed for focused work, to see patients, and for consults between clinicians and clinical staff. We describe the ways practices modified and built new space and provide 2 recommended layouts for practices integrating care based on study findings. CONCLUSION: Physical layout and positioning of professionals' workspace is an important consideration in practices implementing integrated care. Clinicians, researchers, and health-care administrators are encouraged to consider the role of professional proximity and private working space when creating new facilities or redesigning existing space to foster delivery of integrated behavioral health and primary care.

Hadler, J. L., Danila, R. N., Cieslak, P. R., Meek, J. I., Schaffner, W., Smith, K. E., et al. (2015). Emerging infections program—state health department perspective. *Emerging Infectious Diseases, 21*(9), 1510-1515.

Hahn, N. M., Knudsen, B. S., Daneshmand, S., Koch, M. O., Bihrle, R., Foster, R. S., et al. (2015). Neoadjuvant dasatinib for muscle-invasive bladder cancer with tissue analysis of biologic activity. *Urologic Oncology,*

OBJECTIVES: Preclinical urothelial carcinoma models suggest activity of dasatinib, an oral SRC-family kinase (SFK) inhibitor. We sought to determine the feasibility and biologic activity of neoadjuvant dasatinib (Neo-D) in patients with muscle-invasive urothelial carcinoma of the bladder (miUCB) preceding radical cystectomy (RC). MATERIALS AND METHODS: A prospective multisite phase II trial was conducted. Key eligibility criteria included: resectable miUCB (T2-T4a, N0, M0), and Eastern Cooperative Oncology Group performance status 0 to 1. Patients received oral Neo-D 100mg once daily for 28+/-7 days followed by RC 8 to 24 hours after the last dose. The primary end point was feasibility, defined as>/=60% of patients with miUCB completing therapy without treatment-related dose-limiting toxicity (DLT). Pre- and posttreatment tumor immunohistochemistry of phosphorylated SFK (pSFK), Ki-67, and cleaved caspase (Cas)-3 results were analyzed by paired t test. RESULTS: The study completed full accrual with enrollment of 25 patients of whom 23 were evaluable for feasibility. The study achieved its primary end point with 15 patients (65%) completing therapy without treatment-related DLTs. DLTs included: fatigue (n = 2), pulmonary embolism, abdominal pain, supraventricular tachycardia, enteric fistula, hematuria, and dyspnea (n = 1 each). At RC, 5 patients (23%) had<pT2 disease. Analysis of pre- and posttreatment tumors demonstrated significantly decreased pSFK (P = 0.003) but no overall significant changes in Ki-67 or Cas3. In total, 4 cases demonstrated a nonsignificant decrease in Ki-67, of which 3 cases also demonstrated a decrease in pSFK and 2 cases had marginal increase in Cas3. CONCLUSIONS: Neo-D in miUCB patients was feasible and safe. Overall, significant inhibition of pSFK was observed without overall reduction of cellular proliferation or increase of apoptosis, although biologic anti-tumor activity may exist in a small subset of patients. These results highlight the potential utility of the neoadjuvant trial paradigm and suggest that clinical benefit of single-agent SFK inhibition in unselected patients with miUCB is unlikely.

Hall, J., Cohen, D. J., Davis, M., Gunn, R., Blount, A., Pollack, D. A., et al. (2015). Preparing the workforce for behavioral health and primary care integration. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S41-51.

PURPOSE: To identify how organizations prepare clinicians to work together to integrate behavioral health and primary care. METHODS: Observational cross-case comparison study of 19 U.S. practices, 11 participating in Advancing Care Together, and 8 from the Integration Workforce Study. Practices varied in size, ownership, geographic location, and experience delivering integrated care. Multidisciplinary teams collected data (field notes from direct practice observations, semistructured interviews, and online diaries as reported by practice leaders) and then analyzed the data using a grounded theory approach. RESULTS: Organizations had difficulty finding clinicians possessing the skills and experience necessary for working in an integrated practice. Practices newer to integration underestimated the time and resources needed to train and organizationally socialize (onboard) new clinicians. Through trial and error, practices learned that clinicians needed relevant training to work effectively as integrated care teams. Training efforts exclusively targeting behavioral health clinicians (BHCs) and new employees were incomplete if primary care clinicians (PCCs) and others in the practice also lacked experience working with BHCs and delivering integrated care. Organizations' methods for addressing employees' need for additional preparation included hiring a consultant to provide training, sending employees to external training programs, hosting residency or practicum training programs, or creating their own internal training program. Onboarding new employees through the development of training manuals; extensive shadowing processes; and protecting time for ongoing education, mentoring, and support opportunities for new and established clinicians and staff were featured in these internal training programs. CONCLUSION: Insufficient training capacity and practical experience opportunities continue to be major barriers to supplying the workforce needed for effective behavioral health and primary care integration. Until the training capacity grows to meet the demand, practices must put forth considerable effort and resources to train their own employees.

Han, L., & Jensen, J. T. (2015). Does the progestogen used in combined hormonal contraception affect venous thrombosis risk? *Obstetrics and Gynecology Clinics of North America,*

Hansson, J. H., & Watnick, S. (2015). Update on peritoneal dialysis: Core curriculum 2016. *American Journal of Kidney Diseases : The Official Journal of the National Kidney Foundation,*

Heffner, J. E. (2015). Chipping away at duration of therapy for idiopathic acute eosinophilic pneumonia. *Respirology (Carlton, Vic.),*

Higley, M., Beckett, B., Schmahmann, S., Dacey, E., & Foss, E. (2015). Locally aggressive and multifocal phosphaturic mesenchymal tumors: Two unusual cases of tumor-induced osteomalacia. *Skeletal Radiology,*

Tumor-induced osteomalacia (TIO) has long been recognized as a clinical paraneoplastic syndrome. The identification of a unique histopathologic entity, the phosphaturic mesenchymal tumor (PMT), as a distinct etiology for TIO has been a more recent discovery. The majority of published cases describe a solitary, non-aggressive appearing soft tissue or osseous lesions in patients with osteomalacia; aggressive appearing or multifocal lesions appear to be exceedingly rare. These tumors characteristically secrete fibroblast growth factor 23 (FGF23). Elevated serum levels of FGF23 result in phosphate wasting and osteomalacia. In the majority of cases, laboratory abnormalities and clinical signs and symptoms of osteomalacia precede identification of the causative lesion by years. Following diagnosis, complete resection with wide margins to prevent local recurrence is most often curative. Imaging characteristics of PMT are diverse and remain incompletely defined, as the majority of previous publications are outside of the radiologic literature. We present multiple imaging modalities in two cases of patients with debilitating osteomalacia and unusual appearing PMTs: one with a locally aggressive lesion leading to pathologic fracture, the second presenting with exceedingly rare multifocal PMT.

Hirata, M., Shearer, T. R., & Azuma, M. (2015). Hypoxia activates calpains in the nerve fiber layer of monkey retinal explants. *Investigative Ophthalmology & Visual Science, 56*(10), 6049-6057.

PURPOSE: The vascular ischemic hypothesis attributes nerve damage in the retina to decreased blood flow in the ophthalmic artery, reduced oxygenation, and impaired axonal transport. Activation of calpain enzymes contributes to retinal cell death during hypoxia. However, we still do not know in which specific retinal layers calpains are activated. Thus, the purpose of the present study was to investigate where and when calpains are activated in an improved culture model of hypoxic monkey retina. METHODS: Monkey retinal explants were cultured on microporous membranes with the retinal ganglion cell (RGC) side facing up. Explants were

incubated under hypoxic conditions, with or without additional reoxygenation. When it was used, the calpain inhibitor SNJ-1945 was maintained throughout the culture period. Immunohistochemistry and immunoblotting assays for alpha-spectrin, calpains 1 and 2, calpastatin, beta-III tubulin, and gamma-synuclein were performed with specific antibodies. Cell death was assessed by TUNEL staining. RESULTS: Under normoxic conditions, TUNEL-positive cells were minimal in our improved culture conditions. As early as 8 hours after hypoxia, the 150-kDa calpain-specific alpha-spectrin breakdown product appeared in the nerve fiber layer (NFL), where calpains 1 and 2 were localized. TUNEL-positive RGCs then increased at later time periods. The calpain inhibitor SNJ-1945 ameliorated changes induced by hypoxia or hypoxia/reoxygenation. CONCLUSIONS: During hypoxia/reoxygenation in an improved, relevant monkey model, calpains were first activated in the NFL, followed by death of the parent RGCs. This observation suggest that calpain-induced degeneration of retinal nerve fibers may be an underlying mechanism for RGC death in hypoxic retinal neuropathies.

Hirst, J. J., Cumberland, A. L., Shaw, J. C., Bennett, G. A., Kelleher, M. A., Walker, D. W., et al. (2015). Loss of neurosteroid-mediated protection following stress during fetal life. *The Journal of Steroid Biochemistry and Molecular Biology,*

Elevated levels of neurosteroids during late gestation protect the fetal brain from hypoxia/ischaemia and promote neurodevelopment. Suppression of allopregnanolone production during pregnancy leads to the onset of seizure-like activity and potentiates hypoxia-induced brain injury. Markers of myelination are reduced and astrocyte activation is increased. The placenta has a key role in maintaining allopregnanolone concentrations in the fetal circulation and brain during gestation and levels decline markedly after both normal and preterm birth. This leads to the preterm neonate developing in a neurosteroid deficient environment between delivery and term equivalence. The expression of 5alpha-reductases is also lower in the fetus prior to term. These deficiencies in neurosteroid exposure may contribute to the increase in incidence of the adverse patterns of behaviour seen in children that are born preterm. Repeated exposure to glucocorticoid stimulation suppresses 5alpha-reductase expression and allopregnanolone levels in the fetus and results in reduced myelination. Both fetal growth restriction and prenatal maternal stress lead to increased cortisol concentrations in the maternal and fetal circulation. Prenatal stress results in

reduced expression of key GABAA receptor subunits that normally heighten neurosteroid sensitivity. These stressors also result in altered placental allopregnanolone metabolism pathways. These findings suggest that reduced neurosteroid production and action in the perinatal period may contribute to some of the adverse neurodevelopmental and behavioural outcomes that result from these pregnancy compromises. Studies examining perinatal steroid supplementation therapy with non-metabolisable neurosteroid analogues to improve these outcomes are warranted.

Holihan, J. L., Askenasy, E. P., Greenberg, J. A., Keith, J. N., Martindale, R. G., Roth, J. S., et al. (2015). Component separation vs. bridged repair for large ventral hernias: A multi-institutional risk-adjusted comparison, systematic review, and meta-analysis. *Surgical Infections,* BACKGROUND: Repair of large ventral hernia defects is associated with high rates of surgical site occurrences (SSO), including surgical site infection (SSI), site dehiscence, seroma, hematoma, and site necrosis. Two common operative strategies exist: Component separation (CS) with primary fascial closure and mesh reinforcement (PFC-CS) and bridged repair (mesh spanning the hernia defect). We hypothesized that: (1) ventral hernia repair (VHR) of large defects with bridged repair is associated with more SSOs than is PFC, and (2) anterior CS is associated with more SSOs than is endoscopic, perforator-sparing, or posterior CS. METHODS: Part I of this study was a review of a multi-center database of patients who underwent VHR of a defect >/=8 cm from 2010-2011 with at least one month of follow-up. The primary outcome was SSO. The secondary outcome was recurrence. Part II of this study was a systematic review and meta-analysis of studies comparing bridged repair with PFC and studies comparing different kinds of CS. RESULTS: A total of 108 patients were followed for a median of 16 months (range 1-50 months), of whom 84 underwent PFC-CS and 24 had bridged repairs. Unadjusted results demonstrated no differences between the groups in SSO or recurrence; however, the study was underpowered for this purpose. On meta-analysis, PFC was associated with a lower risk of SSO (odds ratio [OR] = 0.569; 95% confidence interval [CI] = 0.34-0.94) and recurrence (OR = 0.138; 95% CI = 0.08-0.23) compared with bridged repair. On multiple-treatments meta-analysis, both endoscopic and perforator-sparing CS were most likely to be the treatments with the lowest risk of SSO and recurrence. CONCLUSIONS: Bridged repair was associated with more

SSOs than was PFC, and PFC should be used whenever feasible. Endoscopic and perforator-sparing CS were associated with the fewest complications; however, these conclusions are limited by heterogeneity between studies and poor methodological quality. These results should be used to guide future trials, which should compare the risks and benefits of each CS method to determine in which setting each technique will give the best results.

Howrey, B. T., Thompson, B. L., Borkan, J., Kennedy, L. B., Hughes, L. S., Johnson, B. H., et al. (2015). Partnering with patients, families, and communities. *Family Medicine, 47*(8), 604-611.

Hryciw, G., Grygoryev, D., Lasarev, M., Ohlrich, A., Dan, C., Madhira, R., et al. (2015). Accelerated ti ions induce autosomal mutations in mouse kidney epithelium at low dose and fluence. *Radiation Research,*

Exposure to high-energy charged particles (HZE ions) at low fluence could significantly affect astronaut health after prolonged missions in deep space by inducing mutations and related cancers. We tested the hypothesis that the mutagenic effects of HZE ions could be detected at low fluence in a mouse model that detects autosomal mutations in vivo. Aprt heterozygous mice were exposed to 0.2, 0.4 and 1.4 Gy of densely ionizing 48Ti ions (1 GeV/amu, LET = 107 keV/mum). We observed a dose-dependent increase in the Aprt mutant fraction in kidney epithelium at the two lowest doses (an average of 1 or 2 particles/cell nucleus) that plateaued at the highest dose (7 particles/cell nucleus). Mutant cells were expanded to determine mutation spectra and translocations affecting chromosome 8, which encodes Aprt. A PCR-based analysis for loss of heterozygosity (LOH) events on chromosome 8 demonstrated a significant shift in the mutational spectrum from Ti ion exposure, even at low fluence, by revealing "radiation signature" mutations in mutant cells from exposed mice. Likewise, a cytogenetic assay for nonreciprocal chromosome 8 translocations showed an effect of exposure. A genome-wide LOH assay for events affecting nonselected chromosomes also showed an effect of exposure even for the lowest dose tested. Considered in their entirety, these results show that accelerated 48Ti ions induce large mutations affecting one or more chromosomes at low dose and fluence.

Hunt, R. H., Camilleri, M., Crowe, S. E., El-Omar, E. M., Fox, J. G., Kuipers, E. J., et al. (2015). The stomach in health and disease. *Gut, 64*(10), 1650-1668.

The stomach is traditionally regarded as a hollow muscular sac that initiates the second phase of digestion. Yet this simple view ignores the fact that it is the most sophisticated endocrine organ with unique physiology, biochemistry, immunology and microbiology. All ingested materials, including our nutrition, have to negotiate this organ first, and as such, the stomach is arguably the most important segment within the GI tract. The unique biological function of gastric acid secretion not only initiates the digestive process but also acts as a first line of defence against food-borne microbes. Normal gastric physiology and morphology may be disrupted by Helicobacter pylori infection, the most common chronic bacterial infection in the world and the aetiological agent for most peptic ulcers and gastric cancer. In this state-of-the-art review, the most relevant new aspects of the stomach in health and disease are addressed. Topics include gastric physiology and the role of gastric dysmotility in dyspepsia and gastroparesis; the stomach in appetite control and obesity; there is an update on the immunology of the stomach and the emerging field of the gastric microbiome. H. pylori-induced gastritis and its associated diseases including peptic ulcers and gastric cancer are addressed together with advances in diagnosis. The conclusions provide a future approach to gastric diseases underpinned by the concept that a healthy stomach is the gateway to a healthy and balanced host. This philosophy should reinforce any public health efforts designed to eradicate major gastric diseases, including stomach cancer.

Huprikar, S., Danziger-Isakov, L., Ahn, J., Kotton, C. N., & Kumar, D. (2015). Reply to: "need to consider full societal impact of hepatitis B virus-positive donors". *American Journal of Transplantation : Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons,*

Iaccarino, J. M., Clark, J., Bolton, R., Kinsinger, L., Kelley, M., Slatore, C. G., et al. (2015). A national survey of pulmonologists' views on low-dose CT screening for lung cancer. *Annals of the American Thoracic Society,*

RATIONALE: Multiple guidelines now recommend low-dose CT (LDCT) screening for lung cancer. Given their central role in the planning of LDCT screening programs, pulmonologists' beliefs about LDCT screening will affect the safety, cost-effectiveness, and success of LDCT screening implementation. OBJECTIVE: To assess pulmonologists' propensity to offer lung cancer screening

and their perceptions about LDCT screening. METHODS: We performed a national web-based survey, administered July 2013 to February 2014, to all staff pulmonologists active in Veterans Health Administration pulmonary clinics. The primary outcome was screening propensity (based on responses to clinical vignettes) in relation to guidelines. We assessed how perceptions of the evidence, trade-offs, and barriers to implementation of LDCT screening programs affected propensity to screen using bivariate and multinomial logistic regression. MEASUREMENTS AND MAIN RESULTS: Of 574 eligible pulmonologists emailed, 286 (49.8%) participated. Approximately half (52.4%) had a propensity for guideline-concordant screening, 22.7% for over-screening, and 24.9% for under-screening. In bivariate analyses, guideline concordance was associated with acceptance of trial evidence, guidelines, and the efficacy of screening. In multivariable models, under-screeners were more likely to cite potential harms of screening (e.g., false positive findings, radiation exposure, incidental findings, unfavorable cost-benefit ratio), as influential factors (RR 3.9, CI 1.5-9.67) and were less influenced by trial evidence and guidelines (RR 0.06, CI 0.02-0.2), as compared to guideline-concordant screeners. Local resource availability did not significantly affect screening propensity, but insufficient infrastructure and personnel were commonly perceived barriers to implementation. CONCLUSIONS: Pulmonologists have varied perceptions of the evidence and trade-offs of LDCT screening, leading to potential for over- and under-screening. To minimize potential harms as LDCT screening is widely implemented, physicians must understand which patients are appropriate candidates and engage patients in a shared decision-making process regarding the trade-offs of LDCT screening.

Ikeda, M., Swide, T., Vayl, A., Lahm, T., Anderson, S., & Hutchens, M. P. (2015). Estrogen administered after cardiac arrest and cardiopulmonary resuscitation ameliorates acute kidney injury in a sex- and age-specific manner. *Critical Care (London, England), 19*, 332-015-1049-8. INTRODUCTION: There is a sex difference in the risk of ischemic acute kidney injury (AKI), and estrogen mediates the protective effect of female sex. We previously demonstrated that preprocedural chronic restoration of physiologic estrogen to ovariectomized female mice ameliorated AKI after cardiac arrest and cardiopulmonary resuscitation (CA/CPR). In the present study, we hypothesized that male mice and aged female mice would benefit from estrogen administration after CA/CPR. We tested the effect of estrogen in a clinically relevant manner by

administrating it after CA/CPR. METHODS: CA/CPR was performed in young (10-15 weeks), middle-aged (43-48 weeks), and aged (78-87 weeks) C57BL/6 male and female mice. Mice received intravenous 17beta-estradiol or vehicle 15 min after resuscitation. Serum chemistries and unbiased stereological assessment of renal injury were completed 24 h after CA. Regional renal cortical blood flow was measured by a laser Doppler, and renal levels of estrogen receptor alpha (ERalpha) and G protein-coupled estrogen receptor (GPER) were evaluated with immunoblotting. RESULTS: Post-arrest estrogen administration reduced injury in young males without significant changes in renal blood flow (percentage reduction compared with vehicle: serum urea nitrogen, 30 %; serum creatinine (sCr), 41 %; volume of necrotic tubules (VNT), 31 %; $P < 0.05$). In contrast, estrogen did not affect any outcomes in young females. In aged mice, estrogen significantly reduced sCr (80 %) and VNT (73 %) in males and VNT (51 %) in females. Serum estrogen levels in aged female mice after CA/CPR were the same as levels in male mice. With age, renal ERalpha was upregulated in females. CONCLUSIONS: Estrogen administration after resuscitation from CA ameliorates renal injury in young males and aged mice in both sexes. Because injury was small, young females were not affected. The protective effect of exogenous estrogen may be detectable with loss of endogenous estrogen in aged females and could be mediated by differences in renal ERs. Post-arrest estrogen administration is renoprotective in a sex- and age-dependent manner.

Iliff, J. J., Goldman, S. A., & Nedergaard, M. (2015). Implications of the discovery of brain lymphatic pathways. *The Lancet.Neurology, 14*(10), 977-979.

Ito, M. K., & Watts, G. F. (2015). Challenges in the diagnosis and treatment of homozygous familial hypercholesterolemia. *Drugs,*

Homozygous familial hypercholesterolemia (HoFH) is a rare, genetic disorder characterized by an absence or impairment of low-density lipoprotein receptor (LDLR) function resulting in significantly elevated low-density lipoprotein cholesterol (LDL-C) levels. The cholesterol exposure burden beginning in utero greatly increases the risk for atherosclerotic cardiovascular disease (ASCVD) and premature death. The genetic heterogeneity of HoFH results in a wide range of LDL-C levels among both untreated and treated patients. Diagnosis of HoFH should, therefore, be

based on a comprehensive evaluation of clinical criteria and not exclusively LDL-C levels. As treatment goals, the European Atherosclerosis Society and International FH Foundation suggest target LDL-C levels of /=50 % from pretreatment levels. Conventional therapy combinations that lower atherogenic lipoproteins levels in the blood, such as statins, ezetimibe, bile acid sequestrants and niacin, as well as lipoprotein apheresis, are usually unable to reduce LDL-C levels to recommended targets. Two recently approved agents that reduce lipoprotein synthesis and secretion by the liver are lomitapide, a microsomal triglyceride transfer protein inhibitor, and mipomersen, an apolipoprotein B antisense oligonucleotide. The newly approved inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9), evolocumab, also shows promise for the management of FH. Because of the extremely high risk for ASCVD, HoFH patients should be identified early.

Jacobs, I., Hectors, S. J., Schabel, M. C., Grull, H., Strijkers, G. J., & Nicolay, K. (2015). Cluster analysis of DCE-MRI data identifies regional tracer-kinetic changes after tumor treatment with high intensity focused ultrasound. *NMR in Biomedicine,*

Evaluation of high intensity focused ultrasound (HIFU) treatment with MRI is generally based on assessment of the non-perfused volume from contrast-enhanced T1 -weighted images. However, the vascular status of tissue surrounding the non-perfused volume has not been extensively investigated with MRI. In this study, cluster analysis of the transfer constant Ktrans and extravascular extracellular volume fraction ve , derived from dynamic contrast-enhanced MRI (DCE-MRI) data, was performed in tumor tissue surrounding the non-perfused volume to identify tumor subregions with distinct contrast agent uptake kinetics. DCE-MRI was performed in CT26.WT colon carcinoma-bearing BALB/c mice before (n = 12), directly after (n = 12) and 3 days after (n = 6) partial tumor treatment with HIFU. In addition, a non-treated control group (n = 6) was included. The non-perfused volume was identified based on the level of contrast enhancement. Quantitative comparison between non-perfused tumor fractions and non-viable tumor fractions derived from NADH-diaphorase histology showed a stronger agreement between these fractions 3 days after treatment (R2 to line of identity = 0.91) compared with directly after treatment (R2 = 0.74). Next, k-means clustering with four clusters was applied to Ktrans and ve parameter values of all significantly enhanced pixels. The fraction of pixels within two clusters,

characterized by a low Ktrans and either a low or high ve , significantly increased after HIFU. Changes in composition of these clusters were considered to be HIFU induced. Qualitative H&E histology showed that HIFU-induced alterations in these clusters may be associated with hemorrhage and structural tissue disruption. Combined microvasculature and hypoxia staining suggested that these tissue changes may affect blood vessel functionality and thereby tumor oxygenation. In conclusion, it was demonstrated that, in addition to assessment of the non-perfused tumor volume, the presented methodology gives further insight into HIFU-induced effects on tumor vascular status. This method may aid in assessment of the consequences of vascular alterations for the fate of the tissue. Copyright (c) 2015 John Wiley & Sons, Ltd.

Jansen, L. A. (2015). Voluntary stopping of eating and drinking (VSED), physician-assisted suicide (PAS), or neither in the last stage of life? PAS: No; VSED: It depends. *Annals of Family Medicine, 13*(5), 410-411.

Jayaram, H., Scawn, R., Pooley, F., Chiang, M., Bunce, C., Strouthidis, N. G., et al. (2015). Long-term outcomes of trabeculectomy augmented with mitomycin C undertaken within the first 2 years of life. *Ophthalmology,*

PURPOSE: To evaluate the long-term effectiveness and safety of mitomycin C (MMC)-augmented trabeculectomy undertaken within the first 2 years of life for the surgical management of glaucoma. DESIGN: Retrospective, consecutive, noncomparative case series. PARTICIPANTS: All children who underwent MMC-augmented trabeculectomy within 2 years of birth between May 2002 and November 2012. METHODS: The medical records of 40 consecutive eyes of 26 children who underwent surgery by a single surgeon were reviewed. Data collected during routine clinical care were analyzed. MAIN OUTCOME MEASURES: Assessment of clinical outcomes included intraocular pressure (IOP), final visual acuity, bleb morphology, surgical complications (early and late), postoperative interventions, and further glaucoma surgery performed. Surgical success was defined as final IOP of 5 mmHg or more and of 21 mmHg or less, with anti-glaucoma medications (qualified success) and without (complete success), stable ocular dimensions and optic disc cupping, and no further glaucoma surgery (including needling) or loss of light perception. Surgical outcomes were evaluated using Kaplan-Meier life table analysis. RESULTS: Forty eyes of

26 children were studied over a mean follow-up period of 62.8 months. Most cases (80%) were of primary congenital glaucoma after failed goniotomy surgery. Cumulative probabilities of survival at 1, 5, and 7 years were 78%, 67%, and 60%, respectively. Of eyes regarded as successful, 96% (25/26 eyes) had controlled IOP without topical medication and 44% achieved visual acuity of 20/40 or better. In only 1 of the 40 eyes did a cystic avascular bleb develop, with all the other eyes being non-cystic in nature (diffuse and elevated or flat) at final follow-up. Sixty-four percent (9/14 eyes) of cases regarded as failures ultimately underwent glaucoma drainage device implantation. CONCLUSIONS: A contemporary pediatric trabeculectomy technique augmented with MMC is an effective procedure in the management of glaucoma within the first 2 years of life, as shown by the successful long-term outcomes and low incidence of sight-threatening complications. Trabeculectomy after failed goniotomy surgery or as a primary surgical intervention may offer a phakic infant with glaucoma an excellent opportunity to achieve long-term control of IOP without medications and may be associated with optimal visual outcomes.

Jennings, H. S., Rao, S. V., Feldman, D. N., Kolansky, D. M., Kutcher, M. A., Baker, N. C., et al. (2015). SCAI core curriculum for adult and pediatric interventional fellowship training in continuous quality assessment and improvement. *Catheterization and Cardiovascular Interventions, 86*(3), 422-431.

Jewell, M., Daunch, W., Bengtson, B., & Mortarino, E. (2015). The development of SERI surgical scaffold, an engineered biological scaffold. *Annals of the New York Academy of Sciences,*
The primary goal of reconstructive and revision surgery is to restore, repair, rebuild, and support damaged, weakened, or absent tissue. There are numerous approaches for soft tissue support and repair, including the use of autologous tissue, human- or animal-derived acellular dermal matrices, absorbable or permanent synthetic mesh, and, now, a new class of bioresorbable protein scaffold. Although many factors influence the choice of surgical approach and the specific product used for soft tissue support and repair, the goal is to improve long-term outcomes while minimizing complications and recurrences requiring further revisional surgery. In this review, the

basic science, clinical characteristics, and clinical applications of SERI(R) Surgical Scaffold, a novel, engineered, highly purified silk product for soft tissue support and repair will be presented.

Jiang, H., Wang, C., Guan, J., Wang, L., & Li, Z. (2015). Changes of spontaneous parthenogenetic activation and development potential of golden hamster oocytes during the aging process. *Acta Histochemica, 117*(1), 104-110.

The golden hamster is an excellent animal experimental model for oocyte research. The hamster oocytes are very useful in clinical examination of human spermatozoan activity. Non-fertile oocytes can lead to time-dependent processes of aging, which will affect the results of human spermatozoa examination. As a consequence there is a need to investigate the aging and anti-aging processes of golden hamster oocytes. In order to study the aging processes and parthenogenetic activation of golden hamster oocytes, in vivo oocytes, oocytes cultured with or without cumulus cells, and oocytes treated with Trichostatin A (TSA) or caffeine were collected and investigated. We found that: (1) spontaneous parthenogenetic activation, developmental potential (cleavage rate), and zona pellucida (ZP) hardening undergo age-dependent changes in in vivo, in vitro, and after TSA or caffeine treatment; (2) in vivo, oocytes became spontaneously parthenogenetic 25 h post-hCG treatment; (3) in vitro, cumulus cells did not significantly increase the parthenogenetic activation rate of cultured hamster oocytes; and (4) TSA or caffeine could delay spontaneous oocyte parthenogenetic activation and the aging processes by at least 5h, but also accelerated the hardening of the ZP. These results define the conditions for the aging and anti-aging processes in golden hamster oocytes. TSA and caffeine play roles in controlling spontaneous activation, which could facilitate the storage and use of golden hamster oocytes for studying processes relevant to human reproduction.

Jones, K. D. (2015). Recommendations for resistance training in patients with fibromyalgia. *Arthritis Research & Therapy, 17*, 258-015-0782-3.

It may seem counter-intuitive to purposely stress muscle in patients who have muscle pain. However, a growing body of evidence challenges the assumption that resistance (strength) training worsens muscle pain in people with fibromyalgia (FM). In fact, the latest evidence indicates that when resistance training is tailored to individual needs, people with FM can obtain

worthwhile improvements in FM severity. Clinicians need a deeper understanding of how resistance training helps people with FM, so as to prescribe more specific, personalized resistance training to their patients.

Kabir, M. M., Ghafoori, E., & Tereshchenko, L. G. (2015). High atrioventricular phase index on near-field intracardiac electrogram is associated with risk of ventricular arrhythmia. *Journal of Electrocardiology,*

The purposes of this study were to characterize and quantify concordance between consecutive atrial and ventricular activation time points through analysis of phases and to explore its association with outcomes in patients with implantable cardioverter-defibrillator (ICD). Patients with structural heart disease and dual-chamber ICDs underwent 5min baseline right ventricular (V) near-field and atrial (A) electrogram (EGM) recording. The cross-dependencies of phase dynamics of the changes in consecutive A (AA') and V (VV') were quantified and the AV phase dependency index was determined. In Cox regression analysis, a high AV phase index (in the highest quartile, >0.259) was significantly associated with higher risk of ventricular tachyarrhythmias (HR 2.84; 95% CI 1.05-7.67; P=0.04). In conclusion, in ICD patients with structural heart disease, high sinus AV phase dependency index on EGM is associated with the risk of ventricular arrhythmia.

Kalra, A., Forman, D. E., & Goodlin, S. J. (2015). Medical decision making for older adults: An international perspective comparing the united states and india. *Journal of Geriatric Cardiology : JGC, 12*(4), 329-334.

There has been a significant decline in cardiovascular morbidity and mortality amidst pervasive advances in care, including percutaneous revascularization, mechanical circulatory support, and transcatheter valvular therapies. While advancing therapies may add significant longevity, they also bring about new end-of-life decision-making challenges for patients and their families who also must weigh the advantages of reduced mortality to the possibility of longer lives consisting of high morbidity, frailty, pain, and poor quality of living. Advance care entails options of withholding or withdrawing therapies, and has become a familiar part of cardiovascular care for older patients in Western countries. However, as advanced cardiovascular practices extend to

developing countries, the interrelated concept of advance care is rarely straight forward as it is affected by local cultural traditions and mores, and can lead to very different inferences and use. This paper discusses the concepts of advance care planning, surrogate decision-making, orders for resuscitation and futility in patients with cardiac disease with comparisons of West to East, focusing particularly on the United States versus India.

Kapeles, M., Gensheimer, M. F., Mart, D. A., Sottero, T. L., Kusano, A. S., Truong, A., et al. (2015). Trimodality treatment of malignant pleural mesothelioma: An institutional review. *American Journal of Clinical Oncology,*

OBJECTIVE: Malignant pleural mesothelioma (MPM) is a deadly disease with varying treatment options. This study retrospectively describes treatment practices at the University of Washington Medical System from 1980 to 2011, and evaluates the impact of trimodality therapy and radiation (photon and neutron) on survival. METHODS: A retrospective study was conducted on patients treated for MPM. Univariate and multivariate methods were utilized to evaluate potential factors associated with survival. Treatments received and baseline characteristics were included. Survival analysis of trimodality therapy was performed using a propensity score method to control for baseline characteristics. RESULTS: Among 78 eligible patients, the median age at diagnosis was 59 years and the median survival was 13.7 months. On multivariate analysis, the significant predictors of improved survival were age, smoking history, location, and receipt of radiation therapy or chemotherapy. In the 48 patients receiving radiation therapy, the difference in survival between neutron therapy and non-neutron therapy patients was not statistically significant: hazard ratio, 1.20 (95% confidence interval, 0.68-2.13), P=0.52. Patients receiving trimodality therapy were more likely to have early-stage disease (60% vs. 30%) and epithelioid histology (86% vs. 58%). In a propensity score-weighted Cox proportional hazards model, trimodality therapy patients had improved overall survival, hazard ratio 0.45, P=0.004, median 14.6 versus 8.6 months. CONCLUSIONS: Trimodality therapy was significantly associated with prolonged survival in patients with MPM, even when adjusting for baseline patient factors. Radiation therapy was associated with improved survival, but the modality of radiation therapy used was not associated with outcome.

Karna, S. K., Rohit, M. K., & Wanchu, A. (2014). Right ventricular thickness as predictor of global myocardial performance in systemic sclerosis: A doppler tissue imaging study. *Indian Heart Journal,*

Kato, T. A., Hashimoto, R., Hayakawa, K., Kubo, H., Watabe, M., Teo, A. R., et al. (2015). The multidimensional anatomy of "modern type depression" in japan: A proposal for a different diagnostic approach to depression beyond the DSM-5. *Psychiatry and Clinical Neurosciences,* Japan's prototype of depression had traditionally been a melancholic depression based on the premorbid personality "shuchaku-kishitsu" proposed by Mitsuzo Shimoda in the 1930s. However since around 2000, a novel form of depression has emerged among youth. Called 'modern type depression (MTD)' by mass media, the term has quickly gained popularity among the general public, though it has not been regarded as an official medical term. Likewise, lack of consensus guidelines for its diagnosis and treatment, and a dearth of scientific literature on MTD has led to confusion when dealing with it in clinical practice in Japan. In this review article, we summarize and discuss the present situation and issues regarding MTD by focusing on historical, diagnostic, psychosocial, and cultural perspectives. We also draw on international perspectives (Kato TA et al. J Affect Dis 2011) that begin to suggest that MTD is a phenomenon that MTD may exist not only in Japan but also in many other countries with different socio-cultural and historical backgrounds. It is therefore of interest to establish whether MTD is a culture-specific phenomenon in Japan or a syndrome that can be classified using international diagnostic criteria as contained in ICD or DSM. We propose a novel diagnostic approach for depression that addresses MTD in order to combat the current confusion about depression under the present diagnostic systems.

Kea, B., & Sun, B. C. -. (2015). Consensus development for healthcare professionals. *Internal and Emergency Medicine, 10*(3), 373-383.

Kendall, B. A., Barker, A. P., Hadley, J. C., Florell, S. R., & Winthrop, K. L. (2015). Disseminated mycobacterial infection after international medical tourism. *Open Forum Infectious Diseases, 2*(2), ofv054.

International travel for the purpose of receiving medical care is increasing. We report a case of disseminated mycobacterial infection after fetal stem cell infusion.

Kichler, J. C., Harris, M. A., & Weissberg-Benchell, J. (2015). Contemporary roles of the pediatric psychologist in diabetes care. *Current Diabetes Reviews, 11*(4), 210-221.

Korthuis, P. T., McGinnis, K. A., Kraemer, K. L., Gordon, A. J., Skanderson, M., Justice, A. C., et al. (2015). Quality of HIV care and mortality rates in HIV-infected patients. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America,*
BACKGROUND: The Patient Protection and Affordable Care Act encourages healthcare systems to track quality-of-care measures; little is known about their impact on mortality rates. The objective of this study was to assess associations between HIV quality of care and mortality rates. METHODS: A longitudinal survival analysis of the Veterans Aging Cohort Study included 3038 human immunodeficiency virus (HIV)-infected patients enrolled between June 2002 and July 2008. The independent variable was receipt of >/=80% of 9 HIV quality indicators (QIs) abstracted from medical records in the 12 months after enrollment. Overall mortality rates through 2014 were assessed from the Veterans Health Administration, Medicare, and Social Security National Death Index records. We assessed associations between receiving >/=80% of HIV QIs and mortality rates using Kaplan-Meier survival analysis and adjusted Cox proportional hazards models. Results were stratified by unhealthy alcohol and illicit drug use. RESULTS: The majority of participants were male (97.5%) and black (66.8%), with a mean (standard deviation) age of 49.0 (8.8) years. Overall, 25.9% reported past-year unhealthy alcohol use and 28.4% reported past-year illicit drug use. During 24 805 person-years of follow-up (mean [standard deviation], 8.2 [3.3] years), those who received >/=80% of QIs experienced lower age-adjusted mortality rates (adjusted hazard ratio, 0.75; 95% confidence interval, .65-.86). Adjustment for disease severity attenuated the association. CONCLUSIONS: Receipt of >/=80% of select HIV QIs is associated with improved survival in a sample of predominantly male, black, HIV-infected patients but was insufficient to overcome adjustment for disease severity. Interventions to ensure high-quality care and address underlying chronic illness may improve survival in HIV-infected patients.

Krey, J. F., Sherman, N. E., Jeffery, E. D., Choi, D., & Barr-Gillespie, P. G. (2015). The proteome of mouse vestibular hair bundles over development. *Scientific Data, 2*, 150047.

Development of the vertebrate hair bundle is a precisely orchestrated event that culminates in production of a tightly ordered arrangement of actin-rich stereocilia and a single axonemal kinocilium. To understand how the protein composition of the bundle changes during development, we isolated bundles from young (postnatal days P4-P6) and mature (P21-P25) mouse utricles using the twist-off method, then characterized their constituent proteins using liquid-chromatography tandem mass spectrometry with data-dependent acquisition. Using MaxQuant and label-free quantitation, we measured relative abundances of proteins in both bundles and in the whole utricle; comparison of protein abundance between the two fractions allows calculation of enrichment in bundles. These data, which are available via ProteomeXchange with identifier PXD002167, will be useful for examining the proteins present in mammalian vestibular bundles and how their concentrations change over development.

Kwit, N., Nelson, C., Kugeler, K., Petersen, J., Plante, L., Yaglom, H., et al. (2015). Human plague — united states, 2015. *Morbidity and Mortality Weekly Report, 64*(33), 918-919.

Labadie, C., Lee, J. -., Rooney, W. D., Jarchow, S., Aubert-Frécon, M., Springer, C. S., et al. (2015). Erratum to myelin water mapping by spatially regularized longitudinal relaxographic imaging at high magnetic fields (magn reson med 2014;71:375-387). *Magnetic Resonance in Medicine,*

Laderas, T., Wu, G., & McWeeney, S. (2015). Between pathways and networks lies context: Implications for precision medicine. *Science Progress, 98*(3), 253-263.

Ladermann, A., Denard, P. J., Boileau, P., Farron, A., Deransart, P., Terrier, A., et al. (2015). Effect of humeral stem design on humeral position and range of motion in reverse shoulder arthroplasty. *International Orthopaedics,*

PURPOSE: The impacts of humeral offset and stem design after reverse shoulder arthroplasty (RSA) have not been well-studied, particularly with regard to newer stems which have a lower humeral inclination. The purpose of this study was to analyze the effect of different humeral stem designs on range of motion and humeral position following RSA. METHODS: Using a three-

dimensional computer model of RSA, a traditional inlay Grammont stem was compared to a short curved onlay stem with different inclinations (155 degrees , 145 degrees , 135 degrees) and offset (lateralised vs medialised). Humeral offset, the acromiohumeral distance (AHD), and range of motion were evaluated for each configuration. RESULTS: Altering stem design led to a nearly 7-mm change in humeral offset and 4 mm in the AHD. Different inclinations of the onlay stems had little influence on humeral offset and larger influence on decreasing the AHD. There was a 10 degrees decrease in abduction and a 5 degrees increase in adduction between an inlay Grammont design and an onlay design with the same inclination. Compared to the 155 degrees model, the 135 degrees model improved adduction by 28 degrees , extension by 24 degrees and external rotation of the elbow at the side by 15 degrees , but led to a decrease in abduction of 9 degrees . When the tray was placed medially, on the 145 degrees model, a 9 degrees loss of abduction was observed. CONCLUSIONS: With varus inclination prostheses (135 degrees and 145 degrees), elevation remains unchanged, abduction slightly decreases, but a dramatic improvement in adduction, extension and external rotation with the elbow at the side are observed.

Lahti, E. (2015). “heart”. *Journal of General Internal Medicine, 30*(3), 374-375.

Lansingh, V. C., Carter, M. J., Eckert, K. A., Winthrop, K. L., Furtado, J. M., & Resnikoff, S. (2015). Affordability of cataract surgery using the big mac prices. *Revista Mexicana De Oftalmologia, 89*(1), 21-30.

Lawrenson, K., Li, Q., Kar, S., Seo, J. H., Tyrer, J., Spindler, T. J., et al. (2015). Cis-eQTL analysis and functional validation of candidate susceptibility genes for high-grade serous ovarian cancer. *Nature Communications, 6*, 8234.

Genome-wide association studies have reported 11 regions conferring risk of high-grade serous epithelial ovarian cancer (HGSOC). Expression quantitative trait locus (eQTL) analyses can identify candidate susceptibility genes at risk loci. Here we evaluate cis-eQTL associations at 47 regions associated with HGSOC risk (P</=10(-5)). For three cis-eQTL associations (P<1.4 x 10(-3), FDR<0.05) at 1p36 (CDC42), 1p34 (CDCA8) and 2q31 (HOXD9), we evaluate the functional role of each candidate by perturbing expression of each gene in HGSOC precursor cells.

Overexpression of HOXD9 increases anchorage-independent growth, shortens population-doubling time and reduces contact inhibition. Chromosome conformation capture identifies an interaction between rs2857532 and the HOXD9 promoter, suggesting this SNP is a leading causal variant. Transcriptomic profiling after HOXD9 overexpression reveals enrichment of HGSOC risk variants within HOXD9 target genes (P=6 x 10(-10) for risk variants (P<10(-4)) within 10 kb of a HOXD9 target gene in ovarian cells), suggesting a broader role for this network in genetic susceptibility to HGSOC.

Lee, C. S., & Auld, J. (2015). Heart failure. A primer. *Critical Care Nursing Clinics of North America,*

Lee, C. S., Hiatt, S. O., Denfeld, Q. E., Mudd, J. O., Chien, C., & Gelow, J. M. (2015). Symptom-hemodynamic mismatch and heart failure event risk. *Journal of Cardiovascular Nursing, 30*(5), 394-402.

Lee-Lin, F., Pedhiwala, N., Nguyen, T., & Menon, U. (2015). Breast health intervention effects on knowledge and beliefs over time among chinese american Immigrants—a randomized controlled study. *Journal of Cancer Education, 30*(3), 482-489.

Leisle, L., Valiyaveetil, F., Mehl, R. A., & Ahern, C. A. (2015). Incorporation of non-canonical amino acids. *Advances in Experimental Medicine and Biology, 869*, 119-151.
In this chapter we discuss the strengths, caveats and technical considerations of three approaches for reprogramming the chemical composition of selected amino acids within a membrane protein. In vivo nonsense suppression in the Xenopus laevis oocyte, evolved orthogonal tRNA and aminoacyl-tRNA synthetase pairs and protein ligation for biochemical production of semisynthetic proteins have been used successfully for ion channel and receptor studies. The level of difficulty for the application of each approach ranges from trivial to technically demanding, yet all have untapped potential in their application to membrane proteins.

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

Li, J., Overall, C. C., Johnson, R. C., Jones, M. B., McDermott, J. E., Heffron, F., et al. (2015). ChIP-seq analysis of the sigmaE regulon of salmonella enterica serovar typhimurium reveals new genes implicated in heat shock and oxidative stress response. *PloS One, 10*(9), e0138466.

The alternative sigma factor sigmaE functions to maintain bacterial homeostasis and membrane integrity in response to extracytoplasmic stress by regulating thousands of genes both directly and indirectly. The transcriptional regulatory network governed by sigmaE in Salmonella and E. coli has been examined using microarray, however a genome-wide analysis of sigmaE-binding sites in Salmonella has not yet been reported. We infected macrophages with Salmonella Typhimurium over a select time course. Using chromatin immunoprecipitation followed by high-throughput DNA sequencing (ChIP-seq), 31 sigmaE-binding sites were identified. Seventeen sites were new, which included outer membrane proteins, a quorum-sensing protein, a cell division factor, and a signal transduction modulator. The consensus sequence identified for sigmaE in vivo binding was similar to the one previously reported, except for a conserved G and A between the -35 and -10 regions. One third of the sigmaE-binding sites did not contain the consensus sequence, suggesting there may be alternative mechanisms by which sigmaE modulates transcription. By dissecting direct and indirect modes of sigmaE-mediated regulation, we found that sigmaE activates gene expression through recognition of both canonical and reversed consensus sequence. New sigmaE regulated genes (greA, luxS, ompA and ompX) are shown to be involved in heat shock and oxidative stress responses.

Lieberman, D., & Allen, J. (2015). New approaches to controlling health care costs: Bending the cost curve for colonoscopy. *JAMA Internal Medicine,* , 1-2.

Lieberman, D., & Mascarenhas, R. (2015). Adenoma detection rate: In search of quality improvement, not just measurement. *Gastrointestinal Endoscopy, 82*(4), 683-685.

Lin, P. (2015). Targeting interleukin-6 for noninfectious uveitis. *Clinical Ophthalmology (Auckland, N.Z.), 9*, 1697-1702.

Interleukin-6 (IL-6) is a pleiotropic cytokine implicated in the pathogenesis of many immune-mediated disorders including several types of non-infectious uveitis. These uveitic conditions include Vogt-Koyanagi-Harada syndrome, uveitis associated with Behcet disease, and sarcoidosis.

This review summarizes the role of IL-6 in immunity, highlighting its effect on Th17, Th1, and plasmablast differentiation. It reviews the downstream mediators activated in the process of IL-6 binding to its receptor complex. This review also summarizes the biologics targeting either IL-6 or the IL-6 receptor, including tocilizumab, sarilumab, sirukumab, olokizumab, clazakizumab, and siltuximab. The target, dosage, potential side effects, and potential uses of these biologics are summarized in this article based on the existing literature. In summary, anti-IL-6 therapy for non-infectious uveitis shows promise in terms of efficacy and side effect profile.

Lindly, O. J., Sinche, B. K., & Zuckerman, K. E. (2015). Variation in educational services receipt among US children with developmental conditions. *Academic Pediatrics, 15*(5), 534-543. OBJECTIVE: To examine the relationship between ease of access to needed community-based services (ease of access) and educational services receipt, and variation in educational services receipt by sociodemographic and need factors among a nationally representative sample of children with autism spectrum disorder (ASD), developmental delay (DD), and/or intellectual disability (ID). METHODS: Data from the 2009-2010 National Survey of Children with Special Health Care Needs were linked to the 2011 Survey of Pathways to Diagnosis and Services on a sample of 3502 US children aged 6 to 17 years with ASD, DD, and/or ID. Descriptive statistics, chi-square tests, and multivariable logistic regression models were used to determine associations of educational services receipt with ease of access and sociodemographic and need factors. RESULTS: Among children with developmental conditions, nearly half (49.7%) lacked easy access to services, and 16.9% did not have an individualized education program (IEP). Among children with an IEP, those with ease of access were more likely to have an IEP that addressed parent concerns about the child's development and education than those unable to easily access services (adjusted odds ratio 2.77; 95% confidence interval 1.71-4.49). Need factors, including functional limitations status, care coordination need, developmental condition type, and early intervention receipt, were significantly associated with educational services receipt. CONCLUSIONS: Cross-systems initiatives facilitating service access remain important to ensuring the developmental needs of children with ASD, DD, and/or ID are met. Increased interprofessional collaboration promoting quality educational services receipt for children diagnosed with developmental conditions may further reduce disparities.

Link, J. M., & Hurlin, P. J. (2015). The activities of MYC, MNT and the MAX-interactome in lymphocyte proliferation and oncogenesis. *Biochimica Et Biophysica Acta, 1849*(5), 554-562.

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

Liu, K., Colangelo, L. A., Daviglus, M. L., Goff, D. C., Pletcher, M., Schreiner, P. J., et al. (2015). Can antihypertensive treatment restore the risk of cardiovascular disease to ideal levels?: The coronary artery risk development in young adults (CARDIA) study and the multi-ethnic study of atherosclerosis (MESA). *Journal of the American Heart Association, 4*(9), 10.1161/JAHA.115.002275.

BACKGROUND: It is unclear whether antihypertensive treatment can restore cardiovascular disease risk to the risk level of persons with ideal blood pressure (BP) levels. METHODS AND RESULTS: Data from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Coronary Artery Risk Development in Young Adults (CARDIA) study were analyzed. Outcomes were compared among participants without or with antihypertensive treatment at 3 BP levels: /=140 or diastolic BP >/=90 mm Hg (systolic BP >/=130 or diastolic BP >/=80 mm Hg for participants with diabetes). Among MESA participants aged >/=50 years at baseline, those with BP /=140 or

diastolic BP >/=90 mm Hg (systolic BP >/=130 or diastolic BP >/=80 mm Hg for participants with diabetes). Among MESA participants aged >/=50 years at baseline, those with BP /=140 or diastolic BP >/=90 mm Hg (systolic BP >/=130 or diastolic BP >/=80 mm Hg for participants with diabetes). Among MESA participants aged >/=50 years at baseline, those with BP 100, and twice the incident cardiovascular disease rate over 9.5 years of follow-up than those with BP 100, and twice the incident cardiovascular disease rate over 9.5 years of follow-up than those with BP 100, and twice the incident cardiovascular disease rate over 9.5 years of follow-up than those with BP 100, and twice the incident cardiovascular disease rate over 9.5 years of follow-up than those with BP 100, and twice the incident cardiovascular disease rate over 9.5 years of follow-up than those with BP 100, and twice the incident cardiovascular disease rate over 9.5 years of follow-up than those with BP 3000 mm Hg-years in 25 years), the increase in left ventricular mass index accelerated. CONCLUSIONS: The data suggest that based on the current approach, antihypertensive treatment cannot restore cardiovascular disease risk to ideal levels. Emphasis should be placed on primordial prevention of BP increases to further reduce cardiovascular disease morbidity and mortality.

Lovejoy, T. I., Heckman, T. G., Sikkema, K. J., Hansen, N. B., & Kochman, A. (2015). Changes in sexual behavior of HIV-infected older adults enrolled in a clinical trial of standalone group psychotherapies targeting depression. *AIDS and Behavior, 19*(1), 1-8.

By 2015, one-half of all HIV-positive persons in the U.S. will be 50-plus years of age, and as many as 30 % of older adults living with HIV/AIDS continue to engage in unprotected sexual intercourse. Contemporary positive prevention models often include mental health treatment as a key component of HIV prevention interventions. This secondary data analysis characterized longitudinal patterns of sexual behavior in HIV-positive older adults enrolled in a randomized controlled trial of group mental health interventions and assessed the efficacy of psychosocial treatments that targeted depression to reduce sexual risk behavior. Participants were 295 HIV-positive adults >/=50 years of age experiencing mild to severe depressive symptoms, randomized to one of three study conditions: a 12-session coping improvement group intervention, a 12-session interpersonal support group intervention, or individual therapy upon request. Approximately one-fifth of participants reported one or more occasions of unprotected

anal or vaginal intercourse with HIV-negative sexual partners or persons of unknown HIV serostatus over the study period. Changes in sexual behavior did not vary by intervention condition, indicating that standalone treatments that target and reduce depression may be insufficient to reduce sexual risk behavior in depressed HIV-positive older adults.

Lovell, P. V., Kasimi, B., Carleton, J., Velho, T. A., & Mello, C. V. (2015). Living without DAT: Loss and compensation of the dopamine transporter gene in sauropsids (birds and reptiles). *Scientific Reports, 5*, 14093.

The dopamine transporter (DAT) is a major regulator of synaptic dopamine (DA) availability. It plays key roles in motor control and motor learning, memory formation, and reward-seeking behavior, is a major target of cocaine and methamphetamines, and has been assumed to be conserved among vertebrates. We have found, however, that birds, crocodiles, and lizards lack the DAT gene. We also found that the unprecedented loss of this important gene is compensated for by the expression of the noradrenaline transporter (NAT) gene, and not the serotonin transporter genes, in dopaminergic cells, which explains the peculiar pharmacology of the DA reuptake activity previously noted in bird striatum. This unexpected pattern contrasts with that of ancestral vertebrates (e.g. fish) and mammals, where the NAT gene is selectively expressed in noradrenergic cells. DA circuits in birds/reptiles and mammals thus operate with an analogous reuptake mechanism exerted by different genes, bringing new insights into gene expression regulation in dopaminergic cells and the evolution of a key molecular player in reward and addiction pathways.

Lutsep, H. L., Lynn, M. J., Cotsonis, G. A., Derdeyn, C. P., Turan, T. N., Fiorella, D., et al. (2015). Does stenting versus aggressive medical therapy for intracranial arterial stenosis support stenting during medical therapy for subpopulations of patients with intracranial arterial stenosis? *Stroke; a Journal of Cerebral Circulation,*

BACKGROUND AND PURPOSE: Although the Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial showed that medical therapy alone was superior to stenting plus medical therapy for preventing recurrent strokes in patients with symptomatic intracranial stenosis, we determined whether SAMMPRIS supported the use of stenting in any

subpopulations of patients with symptomatic intracranial arterial stenosis. METHODS: The primary outcome, 30-day stroke and death and later strokes in the territory of the qualifying artery, was compared in those with and without baseline factors in the 2 treatment arms, percutaneous transluminal angioplasty and stenting (PTAS) plus aggressive medical therapy versus aggressive medical therapy alone. Baseline factors included sex, age, race, diabetes mellitus, hypertension, lipid disorder, smoking status, type of qualifying event, qualifying event hypoperfusion symptoms, use of antithrombotic or proton pump inhibitor at baseline, days to enrollment, old infarcts in the same territory, percent stenosis, other artery stenosis, and location of the symptomatic artery. RESULTS: A total of 451 patients were enrolled, 227 randomized to aggressive medical therapy and 224 to PTAS. Of all variables evaluated, the observed 2-year event rates were higher with PTAS than with aggressive medical therapy in the vast majority and the interaction with treatment was not statistically significant for any of the factors. CONCLUSIONS: The SAMMPRIS results do not provide evidence to support the use of PTAS using the Wingspan stent system compared with medical treatment in any examined subpopulation of patients with symptomatic intracranial stenosis, including those with qualifying event hypoperfusion symptoms. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00576693.

Ma, K. K., Rodriguez, M. I., Cheng, Y. W., Norton, M. E., & Caughey, A. B. (2015). Should cell-free DNA testing be used to target antenatal rhesus immune globulin administration? *Journal of Maternal-Fetal and Neonatal Medicine,*

Madriago, E., Wells, R., Sahn, D. J., Diggs, B. S., Langley, S. M., Woodward, D. J., et al. (2014). Abnormal myocardial blood flow in children with mild/moderate aortic stenosis. *Cardiology in the Young, 25*(7), 1358-1366.

Mahlangu, J. N., Weldingh, K. N., Lentz, S. R., Kaicker, S., Karim, F. A., Matsushita, T., et al. (2015). Changes in the amino acid sequence of the rFVIIa analog, vatreptacog alfa, are associated with clinical immunogenicity. *Journal of Thrombosis and Haemostasis : JTH,*
BACKGROUND: Vatreptacog alfa, a recombinant human factor VIIa (rFVIIa) analog developed to improve the treatment of bleeds in hemophilia patients with inhibitors, differs from native FVIIa

by three amino acid substitutions. In a randomized, double-blind, crossover, confirmatory phase III trial (adept 2), 8/72 (11%) hemophilia A or B patients with inhibitors treated for acute bleeds developed anti-drug antibodies (ADAs) to vatreptacog alfa. OBJECTIVES: To characterize the formation of anti-vatreptacog alfa ADAs in hemophilia patients with inhibitors. PATIENTS AND METHODS: This was a post hoc analysis of adept 2. Immunoglobulin isotype determination, specificity analysis of rFVIIa cross-reactive antibodies, epitope mapping of rFVIIa single mutant analogs and pharmacokinetic (PK) profiling were performed to characterize the ADAs. RESULTS: Immunoglobulin isotyping indicated that the ADAs were of the immunoglobulin G subtype. In epitope mapping, none of the rFVIIa single mutant analogs (V158D, E296V or M298Q) contained the complete antibody epitope, confirming that the antibodies were specific for vatreptacog alfa. In two patients, for whom PK profiling was performed both before and after the development of ADAs, vatreptacog alfa showed a prolonged elimination phase following ADA development. During the follow-up evaluation, the rFVIIa cross-reactivity disappeared after the last vatreptacog alfa exposure, despite continued exposure to rFVIIa as part of standard care. CONCLUSIONS: Results from the vatreptacog alfa phase III trial demonstrate that the specific changes made, albeit relatively small, to the FVIIa molecule alters its clinical immunogenicity.

Mancini, M., El-Gohary, M., Pearson, S., Mcnames, J., Schlueter, H., Nutt, J. G., et al. (2015). Continuous monitoring of turning in parkinson's disease: Rehabilitation potential. *Neurorehabilitation, 37*(1), 3-10.

Marandu, T. F., Oduro, J. D., Borkner, L., Dekhtiarenko, I., Uhrlaub, J., Drabig, A., et al. (2015). Immune protection against virus challenge in aging mice is not affected by latent herpesviral infections. *Journal of Virology,*

Latent herpesvirus infections alter the immune homeostasis. To understand if this results in aging-related loss of immune protection against emerging infections, we challenged old mice carrying latent mouse CMV, HSV-1 and/or MHV-68 with Influenza, WNV or VSV. We observed no increase in mortality or weight-loss over herpesvirus-negative counterparts and a relative, but no

absolute reduction in CD8 responses against acute infections. Therefore, herpesviruses do not appear to increase susceptibility to emerging infections in aging.

Marghoob, A. A., Soyer, H. P., Curiel, C., DaSilva, D., High, W. A., Morrison, L. H., et al. (2015). Standards in dermatologic imaging. *JAMA Dermatology, 151*(8), 819-821.

Martel, M. M., Schimmack, U., Nikolas, M., & Nigg, J. T. (2015). Integration of symptom ratings from multiple informants in ADHD diagnosis: A psychometric model with clinical utility. *Psychological Assessment, 27*(3), 1060-1071.

Masterson Creber, R., Patey, M., Lee, C. S., Kuan, A., Jurgens, C., & Riegel, B. (2015). Motivational interviewing to improve self-care for patients with chronic heart failure: MITI-HF randomized controlled trial. *Patient Education and Counseling,*

OBJECTIVE: The purpose of this study was to test the efficacy of a tailored motivational interviewing (MI) intervention versus usual care for improving HF self-care behaviors, physical HF symptoms and quality of life. METHODS: This is a single-center, randomized controlled trial. Participants were enrolled in the hospital. Immediately after discharge, those in the intervention group received a single home visit and 3-4 follow-up phone calls by a nurse over 90 days. RESULTS: A total of 67 participants completed the study (mean age 62+/-12.8 years), of which 54% were African American, 30% were female, 84% had class III/IV symptoms, and 63% were educated at a high school level or less. There were no differences between the groups in self-care maintenance, self-care confidence, physical HF symptoms, or quality of life at 90 days. CONCLUSION: Patients who received the MI intervention had significant and clinically meaningful improvements in HF self-care maintenance over 90 days that exceeded that of usual care. PRACTICE IMPLICATIONS: These data support the use of a nurse-led MI intervention for improving HF self-care. Identifying methods to improve HF self-care may lead to improved clinical outcomes.

Mata, I. F., Jang, Y., Kim, C. H., Hanna, D. S., Dorschner, M. O., Samii, A., et al. (2015). The RAB39B p.G192R mutation causes X-linked dominant parkinson's disease. *Molecular Neurodegeneration, 10*(1), 50-015-0045-4.

OBJECTIVE: To identify the causal gene in a multi-incident U.S. kindred with Parkinson's disease (PD). METHODS: We characterized a family with a classical PD phenotype in which 7 individuals (5 males and 2 females) were affected with a mean age at onset of 46.1 years (range, 29-57 years). We performed whole exome sequencing on 4 affected and 1 unaffected family members. Sanger-sequencing was then used to verify and genotype all candidate variants in the remainder of the pedigree. Cultured cells transfected with wild-type or mutant constructs were used to characterize proteins of interest. RESULTS: We identified a missense mutation (c.574G > A; p.G192R) in the RAB39B gene that closely segregated with disease and exhibited X-linked dominant inheritance with reduced penetrance in females. The mutation occurred in a highly conserved amino acid residue and was not observed among 87,725 X chromosomes in the Exome Aggregation Consortium dataset. Sequencing of the RAB39B coding region in 587 familial PD cases yielded two additional mutations (c.428C > G [p.A143G] and c.624_626delGAG [p.R209del]) that were predicted to be deleterious in silico but occurred in families that were not sufficiently informative to assess segregation with disease. Experiments in PC12 and SK-N-BE(2)C cells demonstrated that p.G192R resulted in mislocalization of the mutant protein, possibly by altering the structure of the hypervariable C-terminal domain which mediates intracellular targeting. CONCLUSIONS: Our findings implicate RAB39B, an essential regulator of vesicular-trafficking, in clinically typical PD. Further characterization of normal and aberrant RAB39B function might elucidate important mechanisms underlying neurodegeneration in PD and related disorders.

McAbee, J. H., Ragel, B. T., McCartney, S., Jones, G. M., Michael, L. M.,2nd, DeCuypere, M., et al. (2015). Factors associated with career satisfaction and burnout among US neurosurgeons: Results of a nationwide survey. *Journal of Neurosurgery, 123*(1), 161-173.

OBJECT :The object of this study was to identify and quantify predictors of burnout and career satisfaction among US neurosurgeons. METHODS: All US members (3247) of the American Association of Neurological Surgeons (AANS) were invited to participate in a survey between September and December 2012. Responses were evaluated through univariate analysis. Factors independently associated with burnout and career satisfaction were determined using multivariable logistic regression. Subgroup analysis of academic and nonacademic neurosurgeons

was performed as well. RESULTS: The survey response rate was 24% (783 members). The majority of respondents were male, 40-60 years old, in a stable relationship, with children, working in a group or university practice, and trained in a subspecialty. More than 80% of respondents reported being at least somewhat satisfied with their career, and 70% would choose a career in neurosurgery again; however, only 26% of neurosurgeons believed their professional lives would improve in the future, and 52% believed it would worsen. The overall burnout rate was 56.7%. Factors independently associated with both burnout and career satisfaction included achieving a balance between work and life outside the hospital (burnout OR 0.45, satisfaction OR 10.0) and anxiety over future earnings and/or health care reform (burnout OR 1.96, satisfaction OR 0.32). While the burnout rate for nonacademic neurosurgeons (62.9%) was higher than that for academic neurosurgeons (47.7%), academicians who had practiced for over 20 years were less likely to be satisfied with their careers. CONCLUSIONS: The rates of burnout and career satisfaction were both high in this survey study of US neurosurgeons. The negative effects of burnout on the lives of surgeons, patients, and their families require further study and probably necessitate the development of interventional programs at local, regional, and even national levels.

McAllister, M., Lasater, K., Stone, T. E., & Levett-Jones, T. (2014). The reading room: Exploring the use of literature as a strategy for integrating threshold concepts into nursing curricula. *Nurse Education in Practice,*

Messer, L. C., Boone-Heinonen, J., Mponwane, L., Wallack, L., & Thornburg, K. L. (2015). Developmental programming: Priming disease susceptibility for subsequent generations. *Current Epidemiology Reports, 2*(1), 37-51.

Racial and/or ethnic minorities carry the highest burden of many adverse health outcomes intergenerationally We propose a paradigm in which developmental programming exacerbates the effects of racial patterning of adverse environmental conditions, thereby contributing to health disparity persistence. Evidence that developmental programming induces a heightened response to adverse exposures ("second hits") encountered later in life is considered. We evaluated the evidence for the second hit phenomenon reported in animal and human studies

from three domains (air, stress, nutrition). Original research including a gestational exposure and a childhood or adulthood second hit exposure was reviewed. Evidence from animal studies suggest that prenatal exposure to air pollutants is associated with an exaggerated reaction to postnatal air pollution exposure, which results in worse health outcomes. It also indicates offspring exposed to prenatal maternal stress produce an exaggerated response to subsequent stressors, including anxiety and hyper-responsiveness of the hypothalamic-pituitary-adrenal axis. Similarly, prenatal and postnatal Western-style diets induce synergistic effects on weight gain, metabolic dysfunction, and atherosclerotic risk. Cross-domain second hits (e.g., gestational air pollution followed by childhood stressor) were also considered. Suboptimal gestational environments induce exaggerated offspring responses to subsequent environmental and social exposures. These developmental programming effects may result in enhanced sensitivity of ongoing, racially patterned, adverse exposures in race/ethnic minorities, thereby exacerbating health disparities from one generation to the next. Empirical assessment of the hypothesized role of priming processes in the propagation of health disparities is needed. Future social epidemiology research must explicitly consider synergistic relationships among social environmental conditions to which gestating females are exposed and offspring exposures when assessing causes for persistent health disparities.

Meyer, E., Kurian, M. A., & Hayflick, S. J. (2015). *Neurodegeneration with brain iron accumulation: Genetic diversity and pathophysiological mechanisms*

Meyers, K. J., Liu, Z., Millen, A. E., Iyengar, S. K., Blodi, B. A., Johnson, E., et al. (2014). Joint associations of diet, lifestyle, andGenes with age-related MacularDegeneration. *Ophthalmology,*

Meyers, K. J., Liu, Z., Millen, A. E., Iyengar, S. K., Blodi, B. A., Johnson, E., et al. (2015). Joint associations of diet, lifestyle, and genes with age-related macular degeneration. *Ophthalmology,* PURPOSE: Unhealthy lifestyles have been associated with increased odds for age-related macular degeneration (AMD). Whether this association is modified by genetic risk for AMD is unknown and was investigated. DESIGN: Interactions between healthy lifestyles AMD risk genotypes were studied in relation to the prevalence of AMD, assessed 6 years later. PARTICIPANTS: Women 50 to 79 years of age in the Carotenoids in Age-Related Eye Disease Study with exposure and AMD

data (n = 1663). METHODS: Healthy lifestyle scores (0-6 points) were assigned based on Healthy Eating Index scores, physical activity (metabolic equivalent of task hours/week), and smoking pack years assessed in 1994 and 1998. Genetic risk was based on Y402H in complement factor H (CFH) and A69S in age-related maculopathy susceptibility locus 2 (ARMS2). Additive and multiplicative interactions in odds ratios were assessed using the synergy index and a multiplicative interaction term, respectively. MAIN OUTCOME MEASURES: AMD presence and severity were assessed from grading of stereoscopic fundus photographs taken in 2001-2004. AMD was present in 337 women, 91% of whom had early AMD. RESULTS: The odds of AMD were 3.3 times greater (95% confidence interval [CI], 1.8-6.1) in women with both low healthy lifestyle score (0-2) and high-risk CFH genotype (CC), relative to those who had low genetic risk (TT) and high healthy lifestyle scores (4-6). There were no significant additive (synergy index [SI], 1.08; 95% CI, 0.70-1.67) or multiplicative (Pinteraction = 0.94) interactions in the full sample. However, when limiting the sample to women with stable diets before AMD assessment (n = 728) the odds for AMD associated with low healthy lifestyle scores and high-risk CFH genotype were strengthened (odds ratio, 4.6; 95% CI, 1.8-11.6) and the synergy index was significant (SI, 1.34; 95% CI, 1.05-1.70). Adjusting for dietary lutein and zeaxanthin attenuated, and therefore partially explained, the joint association. There were no significant additive or multiplicative interactions for ARMS2 and lifestyle score. CONCLUSIONS: Having unhealthy lifestyles and 2 CFH risk alleles increased AMD risk (primarily in the early stages), in an or additive or greater (synergistic) manner. However, unhealthy lifestyles increased AMD risk regardless of AMD risk genotype.

Mimoto, M. S., Kwon, S., Green, Y. S., Goldman, D., & Christian, J. L. (2015). GATA2 regulates wnt signaling to promote primitive red blood cell fate. *Developmental Biology,*

Primitive erythropoiesis is regulated in a non cell-autonomous fashion across evolution from frogs to mammals. In Xenopus laevis, signals from the overlying ectoderm are required to induce the mesoderm to adopt an erythroid fate. Previous studies in our lab identified the transcription factor GATA2 as a key regulator of this ectodermal signal. To identify GATA2 target genes in the ectoderm required for red blood cell formation in the mesoderm, we used microarray analysis to compare gene expression in ectoderm from GATA2 depleted and wild type embryos. Our analysis

identified components of the non-canonical and canonical Wnt pathways as being reciprocally up- and down-regulated downstream of GATA2 in both mesoderm and ectoderm. We show that up-regulation of canonical Wnt signaling during gastrulation blocks commitment to a hematopoietic fate while down-regulation of non-canonical Wnt signaling impairs erythroid differentiation. Our results are consistent with a model in which GATA2 contributes to inhibition of canonical Wnt signaling, thereby permitting progenitors to exit the cell cycle and commit to a hematopoietic fate. Subsequently, activation of non-canonical Wnt signaling plays a later role in enabling these progenitors to differentiate as mature red blood cells.

Minai, O. A., Nguyen, Q., Mummadi, S., Walker, E., McCarthy, K., & Dweik, R. A. (2015). Heart rate recovery is an important predictor of outcomes in patients with connective tissue disease-associated pulmonary hypertension. *Pulmonary Circulation, 5*(3), 565-576.

Reduced heart rate recovery (HRR) after exercise is associated with increased mortality in cardiac and pulmonary diseases. We sought to evaluate the association between HRR after the 6-minute walk test (6MWT) and outcomes in patients with connective tissue disease-associated pulmonary hypertension (CTD-PH). Data were obtained by review of the medical records. HRR was defined as the difference in heart rate at the end of the 6MWT and after 1 minute (HRR1), 2 minutes (HRR2), and 3 minutes (HRR3) of rest. All patients with pulmonary hypertension and a diagnosis of systemic sclerosis, systemic lupus erythematosus, or mixed connective tissue disease who underwent the 6MWT between August 1, 2009, and October 30, 2011, were included (n = 66). By Kaplan-Meier analysis, HRR1, HRR2, and HRR3 at different cutoff points were all good predictors, with HRR1 of /=19) were unlikely to have a clinical worsening event (HR: 0.1 [95% CI: 0.04-0.5]; P = 0.001], to be hospitalized (HR: 0.1 [95% CI: 0.02-0.5]; P = 0.001), or to die (HR: 0.3 [95% CI: 0.07-0.9]; P = 0.04]. In conclusion, in patients with CTD-PH, abnormal HRR1 (defined as HRR1 of <16) after the 6MWT is a strong predictor of clinical worsening, time to clinical worsening, survival, and hospitalization.

Moldavan, M., Cravetchi, O., Williams, M., Irwin, R. P., Aicher, S. A., & Allen, C. N. (2015). Localization and expression of GABA transporters in the suprachiasmatic nucleus. *The European Journal of Neuroscience,*

GABA is a principal neurotransmitter in the suprachiasmatic hypothalamic nucleus (SCN), the master circadian clock. Despite the importance of GABA and GABA uptake for functioning of the circadian pacemaker, the localization and expression of GABA transporters (GATs) in the SCN has not been investigated. The present studies used Western blot analysis, immunohistochemistry, and electron microscopy to demonstrate the presence of GABA transporter 1 (GAT1) and GABA transporter 3 (GAT3) in the SCN. By light microscopy, GAT1 and GAT3 were co-localized throughout the SCN, but were not expressed in the perikarya of arginine vasopressin- or vasoactive intestinal peptide-immunoreactive (-ir) neurons of adult rats, nor in the neuronal processes labeled with the Neurofilament Heavy Chain. By electron microscopy, GAT1- and GAT3-ir was found in glial processes surrounding unlabeled neuronal perikarya, axons, dendrites, and enveloped symmetric and asymmetric axo-dendritic synapses. Glial Fibrillary Acidic Protein-ir astrocytes grown in cell culture were immunopositive for GAT1 and GAT3 - and both GATs could be observed in the same glial cell. These data demonstrate that synapses in the SCN function as "tripartite" synapses consisting of presynaptic axon terminals, postsynaptic membranes, and astrocytes that contain GABA transporters. This model suggests that astrocytes expressing both GATs may regulate the extracellular GABA, and thereby modulate the activity of neuronal networks in the SCN. This article is protected by copyright. All rights reserved.

Montanaro, A. (2015). Primary immunodeficiency disorders. *Immunology and Allergy Clinics of North America,*

Morgan, R. K., & Cohen, M. S. (2015). A clickable aminooxy probe for monitoring cellular ADP-ribosylation. *ACS Chemical Biology, 10*(8), 1778-1784.

Morgan, T. K., Hanifin, J., Mahmood, M., Larson, B., Baig-Lewis, S., Long, T., et al. (2015). Atopic dermatitis is associated with cervical high risk human papillomavirus infection. *Journal of Lower Genital Tract Disease, 19*(4), 345-349.

OBJECTIVE: High-risk human papillomavirus (hrHPV) infection is more likely to persist and cause cervical cancer in immunosuppressed women. Atopic dermatitis, which is known to affect cell-mediated immunity and skin barrier function, is associated with recalcitrant warts; therefore, we hypothesized that women with atopic dermatitis may be more likely to be positive for hrHPV

infection and progress to high-grade cervical dysplasia. MATERIALS AND METHODS: A retrospective case-control study of 1,160 women who were either positive or negative for hrHPV in their index cervical cytology. Patient age, race, history of atopic dermatitis, allergic rhinitis, smoking, body mass index, socioeconomic status, marital status, hormone contraceptive use, and 2-year clinical outcomes (follow-up hrHPV testing and cervical biopsy results) were recorded. All cases with atopic dermatitis (n = 74) were confirmed by a dermatologist. Analyses were restricted to females with documented clinical follow-up, which yielded 577 hrHPV-positive and 583 hrHPV-negative cases for comparison. Associations were examined by t test, chi test, and multivariate logistic regression. RESULTS: Atopic dermatitis was more common in the hrHPV-positive cases (48/577, 8.3%) compared with HPV-negative controls (26/583, 4.5%, p = .007). Multivariate logistic regression analysis revealed an adjusted odds ratio of 3.75 (95% CI = 1.3-10.9, p = .02) after controlling for significant covariates, such as age and marital status. Smoking was not associated with hrHPV infection, persistence, or high-grade cervical dysplasia in these cases. CONCLUSIONS: Atopic dermatitis is associated with cervical hrHPV infection in adult women.

Nakayasu, E. S., Sydor, M. A., Brown, R. N., Sontag, R. L., Sobreira, T. J. P., Slysz, G. W., et al. (2015). Identification of salmonella typhimurium deubiquitinase ssel substrates by immunoaffinity enrichment and quantitative proteomic analysis. *Journal of Proteome Research, 14*(9), 4029-4038.

Neice, A. (2015). The retreating-stop needle guide as an alternative to variable-angle needle guides. *Journal of Medical Devices, Transactions of the ASME, 9*(1)

Newgard, C. D., & Lewis, R. J. (2015). Missing data: How to best account for what is not known. *Jama, 314*(9), 940-941.

Nonas, S. (2015). Pulmonary manifestations of primary immunodeficiency disorders. *Immunology and Allergy Clinics of North America,*

Oh, G. -., Kim, G., Yoon, J., Kim, G. H., & Kim, S. -. (2015). The E-box-like sterol regulatory element mediates the insulin-stimulated expression of hepatic clusterin. *Biochemical and Biophysical Research Communications, 465*(3), 501-506.

O'Leary, J. G., Orloff, S. L., Levitsky, J., Martin, P., & Foley, D. P. (2015). Keeping high MELD liver transplant candidates alive. *Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society,*
As the mean Model for End-Stage Liver Disease (MELD) score at time of liver transplant continues to increase, it is crucial to implement preemptive strategies to reduce waitlist mortality. We review the most common complications that arise in high MELD patients in an effort to highlight strategies that can maximize survival and successful transplantation. This article is protected by copyright. All rights reserved.

Oliveira, D. C., Rocha, M. G., Gatti, A., Correr, A. B., Ferracane, J. L., & Sinhoret, M. A. (2015). Effect of different photoinitiators and reducing agents on cure efficiency and color stability of resin-based composites using different LED wavelengths. *Journal of Dentistry,*
OBJECTIVES: To evaluate the effect of photoinitiators and reducing agents on cure efficiency and color stability of resin-based composites using different LED wavelengths. METHODS: Model resin-based composites were associated with diphenyl(2,4,6-trimethylbenzoyl) phosphine oxide (TPO), phenylbis(2,4,6-trimethylbenzoyl) phosphine oxide (BAPO) or camphorquinone (CQ) associated with 2-(dimethylamino) ethyl methacrylate (DMAEMA), ethyl 4-(dimethyamino) benzoate (EDMAB) or 4-(N,N-dimethylamino) phenethyl alcohol (DMPOH). A narrow (Smartlite, Dentisply) and a broad spectrum (Bluephase G2, Ivoclar Vivadent) LEDs were used for photo-activation (20J/cm2). Fourier transform infrared spectroscopy (FT-IR) was used to evaluate the cure efficiency for each composite, and CIELab parameters to evaluated color stability (DeltaE00) after aging. The UV-vis absorption spectrophotometric analysis of each photoinitiator and reducing agent was determined. Data were analyzed using two-way ANOVA and Tukey's test for multiple comparisons (alpha=0.05). RESULTS: Higher cure efficiency was found for type-I photoinitiators photo-activated with a broad spectrum light, and for CQ-systems with a narrow band spectrum light, except when combined with an aliphatic amine (DMAEMA). Also, when

combined with aromatic amines (EDMAB and DMPOH), similar cure efficiency with both wavelength LEDs was found. TPO had no cure efficiency when light-cured exclusively with a blue narrowband spectrum. CQ-systems presented higher color stability than type-I photoinitiators, especially when combined with DMPOH. CONCLUSIONS: After aging, CQ-based composites became more yellow and BAPO and TPO lighter and less yellow. However, CQ-systems presented higher color stability than type-I photoinitiators, as BAPO- and TPO-, despite their higher cure efficiency when photo-activated with corresponding wavelength range. CLINICAL SIGNIFICANCE: Color matching is initially important, but color change over time will be one of the major reasons for replacing esthetic restorations; despite the less yellowing of these alternative photoinitiators, camphorquinone presented higher color stability.

Ostrowski, K. A., Polackwich, A. S., Conlin, M. J., Hedges, J. C., & Fuchs, E. F. (2015). Impact on pregnancy of gross and microscopic vasal fluid during vasectomy reversal. *The Journal of Urology, 194*(1), 156-159.

PURPOSE: We compared fertility outcomes with gross and microscopic fluid findings at vasectomy reversal at a high volume vasectomy reversal center. MATERIALS AND METHODS: A retrospective study of a prospective database was performed. All vasectomy reversals were performed by a single surgeon (EFF) between 1978 and 2011. The clinical pregnancy rate was self-reported or determined via patient mailers. Patient and operative findings were determined through database review. We classified vasal fluid as opalescent, creamy, pasty or clear. Intraoperative light microscopy was used to determine if sperm or sperm parts were present and if they were motile. Multivariate analysis was performed evaluating patient age, partner age, years after vasectomy, type of surgery, and gross and microscopic fluid analysis. RESULTS: A total of 2,947 microsurgical vasectomy reversals were reviewed after we excluded reversals performed for post-vasectomy pain. We determined the pregnancy status of 902 (31%) cases. On univariate analysis with respect to pregnancy the presence of motile sperm at vasovasostomy neared statistical significance ($p=0.075$) and there was no difference between bilateral vs unilateral motile sperm. Gross fluid appearance was not statistically significant but we found the order of pregnancy success to be opalescent, creamy, clear then pasty fluid. On multivariate analysis only female partner age and sperm heads only or no sperm seen on light microscopy had statistical

significance (p <0.05). CONCLUSIONS: The presence of motile sperm at vasectomy reversal approaches statistical significance on univariate analysis as a factor that affects clinical pregnancy rates. On multivariate analysis female partner age and microscopic findings of sperm heads only or no sperm are inversely related to pregnancy rates. These data will help counsel couples after vasectomy reversal and reinforce the importance of female partner age.

Pescarus, R., Sharata, A. M., Dunst, C. M., Shlomovitz, E., Swanström, L. L., & Reavis, K. M. (2015). Hill procedure for recurrent GERD post-roux-en-Y gastric bypass. *Surgical Endoscopy and Other Interventional Techniques,*

Peterson, D. S., King, L. A., Cohen, R. G., & Horak, F. B. (2015). Cognitive contributions to freezing of gait in parkinson disease: Implications for physical rehabilitation. *Physical Therapy,*
People with Parkinson's disease (PD) who show freezing of gait also have dysfunction in cognitive domains that interact with mobility. Specifically, freezing of gait is associated with executive dysfunction involving response inhibition, divided/switching attention, and visuospatial function. In fact, the neural control impairments leading to freezing of gait have recently been attributed to higher-level, executive and attentional cortical processes involved in coordinating posture and gait rather than to lower-level, sensorimotor impairments. To date, rehabilitation for freezing of gait primarily focuses on compensatory mobility training to overcome freezing events, such as sensory cueing and voluntary step planning. Recently, a few interventions have focused on restitutive, rather than compensatory, therapy. Given the documented impairments in executive function specific to patients with PD who freeze and increasing evidence of overlap between cognitive and motor function, incorporating cognitive challenges with mobility training may have important benefits for patients with freezing of gait. Thus, we propose a novel theoretical framework for exercise interventions that jointly address both the specific cognitive and mobility challenges of people with PD who freeze.

Pfeiffer, R. F. (2015). Non-motor symptoms in parkinson's disease. *Parkinsonism & Related Disorders,*
With the growing awareness of the presence of non-motor symptoms in Parkinson's disease (PD) has come the realization that these non-motor features play a tremendously important, and sometimes dominant, role in the management and even the diagnosis of the disorder. Despite

this, a reluctance to formally address and treat the non-motor symptoms of PD remains and quality of life for PD patients suffers. This review provides an overview of the impact non-motor symptoms have on persons with PD, along with a brief description of some of the more common non-motor features of PD.

Pflibsen, L., Stang, K. A., Sconce, M. D., Wilson, V. B., Hood, R. L., Meshul, C. K., et al. (2015). Executive function deficits and glutamatergic protein alterations in a progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of parkinson's disease. *Journal of Neuroscience Research,*

Changes in executive function are at the root of most cognitive problems associated with Parkinson's disease. Because dopaminergic treatment does not necessarily alleviate deficits in executive function, it has been hypothesized that dysfunction of neurotransmitters/systems other than dopamine (DA) may be associated with this decrease in cognitive function. We have reported decreases in motor function and dopaminergic/glutamatergic biomarkers in a progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) Parkinson's mouse model. Assessment of executive function and dopaminergic/glutamatergic biomarkers within the limbic circuit has not previously been explored in our model. Our results show progressive behavioral decline in a cued response task (a rodent model for frontal cortex cognitive function) with increasing weekly doses of MPTP. Although within the dorsolateral (DL) striatum mice that had been given MPTP showed a 63% and 83% loss of tyrosine hydroxylase and dopamine transporter expression, respectively, there were no changes in the nucleus accumbens or medial prefrontal cortex (mPFC). Furthermore, dopamine-1 receptor and vesicular glutamate transporter (VGLUT)-1 expression increased in the mPFC following DA loss. There were significant MPTP-induced decreases and increases in VGLUT-1 and VGLUT-2 expression, respectively, within the DL striatum. We propose that the behavioral decline following MPTP treatment may be associated with a change not only in cortical-cortical (VGLUT-1) glutamate function but also in striatal DA and glutamate (VGLUT-1/VGLUT-2) input. (c) 2015 Wiley Periodicals, Inc.

Philippakis, A. A., Azzariti, D. R., Beltran, S., Brookes, A. J., Brownstein, C. A., Brudno, M., et al. (2015). The matchmaker exchange: A platform for rare disease gene discovery. *Human Mutation, 36*(10), 915-921.

Phillips, R. L., Bazemore, A. W., Devoe, J. E., Weida, T. J., Krist, A. H., Dulin, M. F., et al. (2015). A family medicine health technology strategy for achieving the triple aim for US health care. *Family Medicine, 47*(8), 628-635.

Platt, E. J., Durnin, J. P., & Kabat, D. (2015). Short communication: HIV-1 variants that use mouse CCR5 reveal critical interactions of gp120's V3 crown with CCR5 extracellular loop 1. *AIDS Research and Human Retroviruses, 31*(10), 992-998.

Polackwich, A. S., Tadros, N. N., Ostrowski, K. A., Kent, J., Conlin, M. J., Hedges, J. C., et al. (2015). Vasectomy reversal for postvasectomy pain syndrome: A study and literature review. *Urology, 86*(2), 269-272.

Puffer, J. C., Borkan, J., DeVoe, J. E., Davis, A., Phillips, R. L., Green, L. A., et al. (2015). Envisioning a new health care system for america. *Family Medicine, 47*(8), 598-603.

Puljic, A., & Caughey, A. B. (2015). Mild vs. severe intrahepatic cholestasis of pregnancy. *American Journal of Obstetrics and Gynecology,*

Quinn, J. F., Patel, T., Wong, D., Das, S., Freedman, J. E., Laurent, L. C., et al. (2015). Extracellular RNAs: Development as biomarkers of human disease. *Journal of Extracellular Vesicles, 4*, 27495. Ten ongoing studies designed to test the possibility that extracellular RNAs may serve as biomarkers in human disease are described. These studies, funded by the NIH Common Fund Extracellular RNA Communication Program, examine diverse extracellular body fluids, including plasma, serum, urine and cerebrospinal fluid. The disorders studied include hepatic and gastric cancer, cardiovascular disease, chronic kidney disease, neurodegenerative disease, brain tumours, intracranial haemorrhage, multiple sclerosis and placental disorders. Progress to date and the plans for future studies are outlined.

Rahman, Q. A., Tereshchenko, L. G., Kongkatong, M., Abraham, T., Roselle Abraham, M., & Shatkay, H. (2015). Utilizing ECG-based heartbeat classification for hypertrophic cardiomyopathy identification. *IEEE Transactions on Nanobioscience, 14*(5), 505-512.

Rajendran, P., Dashwood, W. M., Li, L., Kang, Y., Kim, E., Johnson, G., et al. (2015). Nrf2 status affects tumor growth, HDAC3 gene promoter associations, and the response to sulforaphane in the colon. *Clinical Epigenetics, 7*(1), 102-015-0132-y. eCollection 2015.

BACKGROUND: The dietary agent sulforaphane (SFN) has been reported to induce nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2)-dependent pathways as well as inhibiting histone deacetylase (HDAC) activity. The current investigation sought to examine the relationships between Nrf2 status and HDAC expression in preclinical and translational studies. RESULTS: Wild type (WT) and Nrf2-deficient (Nrf2(-/+)) mice were treated with the colon carcinogen 1,2-dimethylhydrazine (DMH) followed by 400 ppm SFN in the diet (n = 35 mice/group). WT mice were more susceptible than Nrf2(-/+) mice to tumor induction in the colon. Tumors from WT mice had higher HDAC levels globally and locally on genes such as cyclin-dependant kinase inhibitor 2a (Cdkn2a/p16) that were dysregulated during tumor development. The average tumor burden was reduced by SFN from 62.7 to 26.0 mm(3) in WT mice and from 14.6 to 11.7 mm(3) in Nrf2(-/+) mice. The decreased antitumor activity of SFN in Nrf2(-/+) mice coincided with attenuated Cdkn2a promoter interactions involving HDAC3. HDAC3 knockdown in human colon cancer cells recapitulated the effects of SFN on p16 induction. Human subjects given a broccoli sprout extract supplement (200 mumol SFN equivalents), or reporting more than five cruciferous vegetable servings per week, had increased p16 expression that was inversely associated with HDAC3 in circulating peripheral blood mononuclear cells (PBMCs) and in biopsies obtained during screening colonoscopy. CONCLUSIONS: Nrf2 expression varies widely in both normal human colon and human colon cancers and likely contributes to the overall rate of tumor growth in the large intestine. It remains to be determined whether this influences global HDAC protein expression levels, as well as local HDAC interactions on genes dysregulated during human colon tumor development. If corroborated in future studies, Nrf2 status might serve as a biomarker of HDAC inhibitor efficacy in clinical trials using single agent or combination modalities to slow, halt, or regress the progression to later stages of solid tumors and hematological malignancies.

Rao, V. H., Vogel, K., Yanagida, J. K., Marwaha, N., Kandel, A., Trempus, C., et al. (2015). Erbb2 up-regulation of ADAM12 expression accelerates skin cancer progression. *Molecular Carcinogenesis, 54*(10), 1026-1036.

Raychev, R., Jahan, R., Liebeskind, D., Clark, W., Nogueira, R. G., Saver, J., et al. (2015). Determinants of intracranial hemorrhage occurrence and outcome after neurothrombectomy therapy: Insights from the solitaire FR with intention for thrombectomy randomized trial. *AJNR.American Journal of Neuroradiology,*

BACKGROUND AND PURPOSE: Intracranial hemorrhage is the most dreaded complication of neurothrombectomy therapy for acute ischemic stroke. The determinants of intracranial hemorrhage and its impact on clinical course remain incompletely delineated. The purpose of this study is to further investigate the clinical and procedural factors leading to intracranial hemorrhage and to define the clinical impact of different hemorrhagic subtypes. MATERIALS AND METHODS: We analyzed data prospectively collected in the Solitaire FR With Intention for Thrombectomy randomized clinical trial. A multivariable logistic regression model was used to identify independent clinical, imaging, and procedural predictors of any intracranial hemorrhage and of 7 intracranial hemorrhage subtypes. Univariate analysis was used to determine the impact of each of the intracranial hemorrhage subtypes on clinical outcome. RESULTS: Among the 144 enrolled patients, any radiologic intracranial hemorrhage (21.3% versus 38.2%, P = .035), symptomatic intracranial hemorrhage (1.1% versus 10.9%, P = .012), and subarachnoid hemorrhage (2.2% versus 12.7%, P = .027) occurred less frequently in the Solitaire FR than in the Merci retriever arms. The most common independent determinant of hemorrhage occurrence was rescue therapy with intra-arterial rtPA, which was associated with any intracranial hemorrhage and 4 subtypes and tended to be used more frequently in the Merci group (10.9% versus 3.4%; P = .09). Among the hemorrhage subtypes, basal ganglionic hemorrhage had the strongest impact on good clinical outcome at 90 days (OR, 0.30; P = .025) and was associated with higher reperfusion, prolonged time to treatment, and rescue therapy with intra-arterial rtPA. CONCLUSIONS: Intracranial hemorrhage, especially subarachnoid and symptomatic intracerebral hemorrhage, occurs less frequently with the Solitaire FR than the Merci retriever, in part due to

less frequent use of rescue therapy with intra-arterial rtPA. Basal ganglionic hemorrhage strongly affects clinical outcome and is distinctively related to late reperfusion.

Read, K. B., Sheehan, J. R., Huerta, M. F., Knecht, L. S., Mork, J. G., Humphreys, B. L., et al. (2015). Sizing the problem of improving discovery and access to NIH-funded data: A preliminary study. *Plos One, 10*(7)

Riddle, M. C., Yki-Järvinen, H., Bolli, G. B., Ziemen, M., Muehlen-Bartmer, I., Cissokho, S., et al. (2015). One-year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/ml compared with 100 U/ml in people with type 2 diabetes using basal plus meal-time insulin: The EDITION 1 12-month randomized trial, including 6-month extension. *Diabetes, Obesity and Metabolism, 17*(9), 835-842.

Rising, M. L. (2015). Truth telling as an element of culturally competent care at end of life. *Journal of Transcultural Nursing : Official Journal of the Transcultural Nursing Society / Transcultural Nursing Society,*

PURPOSE: Nondisclosure of terminal prognosis in the context of intercultural interactions can cause moral distress among health care providers guided exclusively by informed consent. However, cultural humility can show that revealing and withholding prognostic information are two equally valid paths to the goal of protecting the patient from harm. DESIGN: Assumptions and history giving rise to the preference for truth telling in the United States(US) are examined. Principles of biomedical ethics are described within the context of US, Chinese, and Latin American cultures. The process of cultural competence in the delivery of health care services is explained and introduces the concept of cultural humility. IMPLICATIONS FOR PRACTICE: By focusing more on biases and assumptions brought forth from the dominant culture, health care providers may experience less moral distress and convey increased caring in the context of intercultural interactions and nondisclosure of prognosis of a terminal illness.

Robinson, K. A., Chou, R., Berkman, N. D., Newberry, S. J., Fu, R., Hartling, L., et al. (2015). Twelve recommendations for integrating existing systematic reviews into new reviews: EPC guidance. *Journal of Clinical Epidemiology,*

Rosenbaum, J. T., Choi, D., Wong, A., Wilson, D. J., Grossniklaus, H. E., Harrington, C. A., et al. (2015). The role of the immune response in the pathogenesis of thyroid eye disease: A reassessment. *PloS One, 10*(9), e0137654.

BACKGROUND: Although thyroid eye disease is a common complication of Graves' disease, the pathogenesis of the orbital disease is poorly understood. Most authorities implicate the immune response as an important causal factor. We sought to clarify pathogenesis by using gene expression microarray. METHODS: An international consortium of ocular pathologists and orbital surgeons contributed formalin fixed orbital biopsies. RNA was extracted from orbital tissue from 20 healthy controls, 25 patients with thyroid eye disease (TED), 25 patients with nonspecific orbital inflammation (NSOI), 7 patients with sarcoidosis and 6 patients with granulomatosis with polyangiitis (GPA). Tissue was divided into a discovery set and a validation set. Gene expression was quantified using Affymetrix U133 Plus 2.0 microarrays which include 54,000 probe sets. RESULTS: Principal component analysis showed that gene expression from tissue from patients with TED more closely resembled gene expression from healthy control tissue in comparison to gene expression characteristic of sarcoidosis, NSOI, or granulomatosis with polyangiitis. Unsupervised cluster dendrograms further indicated the similarity between TED and healthy controls. Heat maps based on gene expression for cytokines, chemokines, or their receptors showed that these inflammatory markers were associated with NSOI, sarcoidosis, or GPA much more frequently than with TED. CONCLUSION: This is the first study to compare gene expression in TED to gene expression associated with other causes of exophthalmos. The juxtaposition shows that inflammatory markers are far less characteristic of TED relative to other orbital inflammatory diseases.

Rosenbaum, J. T., Lin, P., & Asquith, M. (2015). The microbiome, HLA, and the pathogenesis of uveitis. *Japanese Journal of Ophthalmology,*

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

Rosenstein, M. G., & Caughey, A. B. (2015). Reply: To PMID 24909340. *American Journal of Obstetrics and Gynecology, 213*(1), 112.

Rubenstein, J. H., Lieberman, D., Fennerty, B., & Gellad, Z. F. (2015). Measuring the quality of barrett's esophagus management with measures that are high quality. *Gastroenterology,*

Rudmik, L., Smith, T. L., Mace, J. C., Schlosser, R. J., Hwang, P. H., & Soler, Z. M. (2015). Productivity costs decrease after endoscopic sinus surgery for refractory chronic rhinosinusitis. *The Laryngoscope,*

OBJECTIVES/HYPOTHESIS: The primary objective of this pilot study was to define the change in productivity costs following endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS). Secondary objectives were to identify CRS-related characteristics that may influence the degree of productivity improvement after ESS. STUDY DESIGN: Prospective, multi-institutional, observational cohort study. METHODS: The human capital approach was used to define productivity costs. Annual absenteeism, presenteeism, and lost leisure time were quantified to define annual lost productive time (LPT). LPT was monetized using the annual daily wage rates obtained from the 2012 US Census and the 2013 US Department of Labor statistics. RESULTS: Twenty-seven patients with refractory CRS who underwent ESS were followed for a mean of 15 months (range, 8-25 months). Following ESS, there were improvements in annual absenteeism (22 days reduced to 3 days), annual presenteeism (41 days reduced to 19 days), and annual household days lost (12 days reduced to 6 days). Overall, the preoperative productivity costs were reduced after ESS ($9,190 vs. $3,373, respectively; P < .001). CONCLUSIONS: Daily productivity is negatively impacted by the presence of CRS. The outcomes from this study provide the first insights into the reduced productivity costs associated with receiving ESS for refractory CRS. Future studies with larger sample sizes will need to validate the results from this pilot study. LEVEL OF EVIDENCE: 2c Laryngoscope, 2015.

Rudmik, L., Soler, Z. M., Mace, J. C., DeConde, A. S., Schlosser, R. J., & Smith, T. L. (2015). Using preoperative SNOT-22 score to inform patient decision for endoscopic sinus surgery. *The Laryngoscope, 125*(7), 1517-1522.

OBJECTIVES/HYPOTHESIS: The purpose of this study is to improve patient understanding of

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

Ruskin, K. J., Caldwell, J. A., Caldwell, J. L., & Boudreau, E. A. (2015). Screening for sleep apnea in morbidly obese pilots. *Aerospace Medicine and Human Performance, 86*(9), 835-841. BACKGROUND: Debate regarding the merits of screening pilots for sleep apnea has been stimulated by recently issued guidance from the Federal Aviation Administration. It has long been appreciated that sleep apnea results in poor quality sleep, and that poor quality sleep is associated with daytime fatigue and decrements in performance. However, the relationship between sleep apnea and poor performance, including risk for accidents is not as well understood. Good quality data are available for commercial truck drivers and have helped influence transportation policy, but there is a lack of pilot specific data. The purpose of this article is to review the basic epidemiology, pathophysiology, and treatment of sleep apnea, including major risk factors for apnea, such as body mass index (BMI), and to look at what is known about

the impact of sleep apnea on performance in transportation related occupations. While pilot specific data may be lacking, good quality data for commercial truckers are available and can be used to formulate rational public policy with the goal of improving aviation safety. This article was reviewed by the Council of the Aerospace Medical Association and approved as a position paper of the Association. Ruskin KJ, Caldwell JA, Caldwell JL, Boudreau EA. Screening for sleep apnea in morbidly obese pilots. Aerosp Med Hum Perform. 2015; 86(9):835-841.

Russell, T. D., Jindal, S., Agunbiade, S., Gao, D., Troxell, M., Borges, V. F., et al. (2015). Myoepithelial cell differentiation markers in ductal carcinoma in situ progression. *The American Journal of Pathology,*

We describe a preclinical model that investigates progression of early-stage ductal carcinoma in situ (DCIS) and report that compromised myoepithelial cell differentiation occurs before transition to invasive disease. Human breast cancer MCF10DCIS.com cells were delivered into the mouse mammary teat by intraductal injection in the absence of surgical manipulations and accompanying wound-healing confounders. DCIS-like lesions developed throughout the mammary ducts with full representation of human DCIS histologic patterns. Tumor cells were incorporated into the normal mammary epithelium, developed ductal intraepithelial neoplasia and DCIS, and progressed to invasive carcinoma, suggesting the model provides a rigorous approach to study early stages of breast cancer progression. Mammary glands were evaluated for myoepithelium integrity with immunohistochemical assays. Progressive loss of the myoepithelial cell differentiation markers p63, calponin, and alpha-smooth muscle actin was observed in the mouse myoepithelium surrounding DCIS-involved ducts. p63 loss was an early indicator, calponin loss intermediate, and alpha-smooth muscle actin a later indicator of compromised myoepithelium. Loss of myoepithelial calponin was specifically associated with gain of the basal marker p63 in adjacent tumor cells. In single time point biopsies obtained from 16 women diagnosed with pure DCIS, a similar loss in myoepithelial cell markers was observed. These results suggest that further research is warranted into the role of myoepithelial cell p63 and calponin expression on DCIS progression to invasive disease.

Russo, S., Blackstock, A. W., Herman, J. M., Abdel-Wahab, M., Azad, N., Das, P., et al. (2015). ACR appropriateness criteria(R) local excision in early stage rectal cancer. *American Journal of Clinical Oncology, 38*(5), 520-525.

Low anterior resection or abdominoperineal resection are considered standard treatments for early rectal cancer but may be associated with morbidity in selected patients who are candidates for early distal lesions amenable to local excision (LE). The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 3 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment. The panel recognizes the importance of accurate staging to identify patients who may be candidates for a LE approach. Patients who may be candidates for LE alone include those with small, low-lying T1 tumors, without adverse pathologic features. Several surgical approaches can be utilized for LE however none include lymph node evaluation. Adjuvant radiation+/-chemotherapy may be warranted depending on the risk of nodal metastases. Patients with high-risk T1 tumors, T2 tumors not amenable to radical surgery may also benefit from adjuvant treatment; however, patients with positive margins or T3 lesions should be offered abdominoperineal resection or low anterior resection. Neoadjuvant radiation+/-chemotherapy followed by LE in higher risk patients results in excellent local control, but it is not clear if this approach reduces recurrence rates over surgery alone.

Sahn, D. J. (2015). Meet our editorial board member. *Current Medical Imaging Reviews, 11*(4)

Samet, J. M., Coultas, D., & Raghu, G. (2015). Idiopathic pulmonary fibrosis: Tracking the true occurrence is challenging. *The European Respiratory Journal, 46*(3), 604-606.

Sanders, S. J., He, X., Willsey, A. J., Ercan-Sencicek, A. G., Samocha, K. E., Cicek, A. E., et al. (2015). Insights into autism spectrum disorder genomic architecture and biology from 71 risk loci. *Neuron, 87*(6), 1215-1233.

Analysis of de novo CNVs (dnCNVs) from the full Simons Simplex Collection (SSC) (N = 2,591 families) replicates prior findings of strong association with autism spectrum disorders (ASDs) and confirms six risk loci (1q21.1, 3q29, 7q11.23, 16p11.2, 15q11.2-13, and 22q11.2). The addition of published CNV data from the Autism Genome Project (AGP) and exome sequencing data from the SSC and the Autism Sequencing Consortium (ASC) shows that genes within small de novo deletions, but not within large dnCNVs, significantly overlap the high-effect risk genes identified by sequencing. Alternatively, large dnCNVs are found likely to contain multiple modest-effect risk genes. Overall, we find strong evidence that de novo mutations are associated with ASD apart from the risk for intellectual disability. Extending the transmission and de novo association test (TADA) to include small de novo deletions reveals 71 ASD risk loci, including 6 CNV regions (noted above) and 65 risk genes (FDR </= 0.1).

Saultz, J. W. (2015). Family medicine for america's health: A special issue of family medicine. *Family Medicine, 47*(8), 593-594.

Saultz, J. W., Jones, S. M., McDaniel, S. H., Bagley, B., McCormally, T., Marker, J. E., et al. (2015). A new foundation for the delivery and financing of american health care. *Family Medicine, 47*(8), 612-619.

BACKGROUND AND OBJECTIVES: For the past decade, primary care practices across America have worked to implement a practice model called the Patient-Centered Medical Home (PCMH) to revitalize practice, better support clinicians and patients, improve efficiency, and facilitate growth in primary care capacity. In spite of substantial progress, this work has not been matched by sufficient change in the payment system to allow these goals to be accomplished. Nevertheless, improving the quality and availability of primary care remains essential to achieving the goals of the Triple Aim (better health care, better population health, and containment of health care costs). For this to occur, the PCMH model of care must be further refined, and the payment system for primary care must be completely restructured. The need for these changes is urgent. In October 2014, the discipline of family medicine announced a comprehensive strategic plan called Family Medicine for America's Health (FMAHealth). FMAHealth proposes to expand the PCMH care model by fully integrating our nation's behavioral/mental health, public health, and

primary care systems to create a new foundation for American health care. Accomplishing these ambitious goals will require a broad coalition of private and public interests across the health care disciplines as well as patients, communities, government, and businesses. These changes require additional infrastructure that existing financing systems do not adequately support, so comprehensive payment reform is essential for large-scale dissemination and sustainability of this model. The new payment model must reward value rather than volume of service and must provide a secure financial foundation for practices designed to care for patients and communities at affordable costs.

Saute, J. A., Giugliani, R., Merkens, L. S., Chiang, J. P. -., DeBarber, A. E., & de Souza, C. F. M. (2015). Look carefully to the heels! A potentially treatable cause of spastic paraplegia. *Journal of Inherited Metabolic Disease, 38*(2), 363-364.

Schousboe, J. T., Vo, T., Taylor, B. C., Cawthon, P. M., Schwartz, A. V., Bauer, D. C., et al. (2015). Prediction of incident major osteoporotic and hip fractures by trabecular bone score (TBS) and prevalent radiographic vertebral fracture in older men. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research,*
Trabecular Bone Score (TBS) has been shown to predict major osteoporotic (clinical vertebral, hip, humerus, and wrist) and hip fractures in post-menopausal women and older men, but the association of TBS with these incident fractures in men independent of prevalent radiographic vertebral fracture is unknown. TBS was estimated on AP spine DXA scans obtained at the baseline visit for 5,979 men age >/=65 years enrolled in MrOS and its association with incident major osteoporotic and hip fractures estimated with proportional hazards models. Model discrimination was tested with Harrell's C-statistic and with a categorical net reclassification improvement index, using 10-year risk cutpoints of 20% for major osteoporotic and 3% for hip fractures. For each standard deviation decrease in TBS, there were hazard ratios of 1.27 (95% C.I. 1.17 to 1.39) for major osteoporotic fracture, and 1.20 (95% C.I. 1.05 to 1.39) for hip fracture, adjusted for FRAX with BMD 10 year fracture risks and prevalent radiographic vertebral fracture. In the same model, those with prevalent radiographic vertebral fracture compared to those without prevalent radiographic vertebral fracture had hazard ratios of 1.92 (95% C.I. 1.49

to 2.48) for major osteoporotic fracture and 1.86 (95% C.I. 1.26 to 2.74) for hip fracture. There were improvements of 3.3%, 5.2%, and 6.2%, respectively, of classification of major osteoporotic fracture cases when TBS, prevalent radiographic vertebral fracture status, or both were added to FRAX with BMD and age, with minimal loss of correct classification of non-cases. Neither TBS nor prevalent radiographic vertebral fracture improved discrimination of hip fracture cases or non-cases. In conclusion, TBS and prevalent radiographic vertebral fracture are associated with incident major osteoporotic fractures in older men independent of each other and FRAX 10 year fracture risks, and these data support their use in conjunction with FRAX for fracture risk assessment in older men. This article is protected by copyright. All rights reserved.

Selvam, A. P., Prasad, S., Barrett, T. W., & Kazmierczak, S. C. (2015). Electrical nanowell diagnostics sensors for rapid and ultrasensitive detection of prostate-specific antigen. *Nanomedicine, 10*(16), 2527-2536.

Serrano, C., Wang, Y., Mariño-Enríquez, A., Lee, J. -., Ravegnini, G., Morgan, J. A., et al. (2015). KRAS and KIT gatekeeper mutations confer polyclonal primary imatinib resistance in GI stromal tumors: Relevance of concomitant phosphatidylinositol 3-kinase/AKT dysregulation. *Journal of Clinical Oncology, 33*(22), e93-e96.

Servan-Mori, E., Sosa-Rubi, S. G., Najera-Leon, E., & Darney, B. G. (2015). Timeliness, frequency and content of antenatal care: Which is most important to reducing indigenous disparities in birth weight in mexico? *Health Policy and Planning,*

This article examines the role of components of adequate antenatal care (ANC) in disparities in birth weight between indigenous and non-indigenous women in Mexico. We estimate the potential for added weight gain among indigenous infants if their mothers received timely, frequent (>/=4 visits) and complete ANC (>/=75% of recommended processes of care). We used population-based survey data (2012; N = 6612 women 12-49). We applied quantile regression to examine heterogeneity of the association between adequate ANC, indigenous ethnicity and birth weight across quantiles of the birth weight distribution. A greater proportion of indigenous women reported a low-birth weight infant (/=75% of the content of ANC compared with those that did not have access: approximately 180 and 260 g are gained in both quantiles 0.05 and 0.10,

respectively. This means that the smallest indigenous newborns could potentially reach 2.36 kg (from 1.86 kg), close to the normal weight threshold. The frequency of ANC was positively associated with birth weight for all women but complete ANC appears to differentially affect indigenous women at the bottom of the birth weight distribution. The marginal gains obtained among indigenous newborns that received complete ANC compared with indigenous/non-indigenous newborns did not receive it, is particularly important in low-birth weight quantiles. Delivering basic processes of ANC may therefore have the potential to impact the highest risk women and help them to overcome the low-birth weight threshold.

Shain, A. H., Garrido, M., Botton, T., Talevich, E., Yeh, I., Sanborn, J. Z., et al. (2015). Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway. *Nature Genetics, 47*(10), 1194-1199. Desmoplastic melanoma is an uncommon variant of melanoma with sarcomatous histology, distinct clinical behavior and unknown pathogenesis. We performed low-coverage genome and high-coverage exome sequencing of 20 desmoplastic melanomas, followed by targeted sequencing of 293 genes in a validation cohort of 42 cases. A high mutation burden (median of 62 mutations/Mb) ranked desmoplastic melanoma among the most highly mutated cancers. Mutation patterns strongly implicate ultraviolet radiation as the dominant mutagen, indicating a superficially located cell of origin. Newly identified alterations included recurrent promoter mutations of NFKBIE, encoding NF-kappaB inhibitor varepsilon (IkappaBvarepsilon), in 14.5% of samples. Common oncogenic mutations in melanomas, in particular in BRAF (encoding p.Val600Glu) and NRAS (encoding p.Gln61Lys or p.Gln61Arg), were absent. Instead, other genetic alterations known to activate the MAPK and PI3K signaling cascades were identified in 73% of samples, affecting NF1, CBL, ERBB2, MAP2K1, MAP3K1, BRAF, EGFR, PTPN11, MET, RAC1, SOS2, NRAS and PIK3CA, some of which are candidates for targeted therapies.

Shepard, J. E., Douglas, A., Phillipi, C. A., & Guzman-Cottrill, J. A. (2015). Free vaccines for parents program: A novel (and successful) pediatric resident advocacy project. *Academic Pediatrics, 15*(5), 476-479.

Shi, Z., Li, B., & Brooks, V. L. (2015). Role of the paraventricular nucleus of the hypothalamus in the sympathoexcitatory effects of leptin. *Hypertension,*

Leptin binds to receptors in multiple hypothalamic nuclei to increase sympathetic nerve activity; however, the neurocircuitry is unclear. Here, using anesthetized male Sprague-Dawley rats, we investigated the role of the paraventricular nucleus of the hypothalamus. Intracerebroventricular injection of leptin slowly increased lumbar sympathetic nerve activity (LSNA), heart rate, mean arterial pressure, and baroreflex control of LSNA and heart rate. Inhibition of the paraventricular nucleus with muscimol completely reversed leptin's effects. Blockade of paraventricular melanocortin 3/4 receptors with SHU9119 or ionotropic glutamate receptors with kynurenate, alone or together, each partially reversed the effects of leptin, implicating increased activation of glutamate and melanocortin 3/4 receptors. Conversely, although blockade of neuropeptide Y Y1 receptors in the paraventricular nucleus increased LSNA, mean arterial pressure, and heart rate, these responses were prevented by intracerebroventricular or arcuate nucleus injections of leptin, suggesting that, at least in part, leptin also increases sympathetic nerve activity by suppression of tonic neuropeptide Y inhibitory inputs from the arcuate nucleus. Injection of the melanocortin 3/4 receptor agonist melanotan-II into the paraventricular nucleus increased LSNA, mean arterial pressure, and heart rate only after blockade of neuropeptide Y Y1 receptors. Therefore, we conclude that leptin increases LSNA in part via increased glutamatergic and alpha-melanocyte-stimulating hormone drive of paraventricular sympathoexcitatory neurons, the latter of which requires simultaneous withdrawal of tonic neuropeptide Y inhibition.

Simuni, T., Caspell-Garcia, C., Coffey, C., Chahine, L. M., Lasch, S., Oertel, W. H., et al. (2015). Correlates of excessive daytime sleepiness in de novo parkinson's disease: A case control study. *Movement Disorders, 30*(10), 1371-1381.

Skoff, T. H., Baumbach, J., & Cieslak, P. R. (2015). Tracking pertussis and evaluating control measures through enhanced pertussis surveillance, emerging infections program, united states. *Emerging Infectious Diseases, 21*(9), 1568-1573.

Slee, S. J., & David, S. V. (2015). Rapid task-related plasticity of spectrotemporal receptive fields in the auditory midbrain. *The Journal of Neuroscience : The Official Journal of the Society for*

Neuroscience, 35(38), 13090-13102.

Previous research has demonstrated that auditory cortical neurons can modify their receptive fields when animals engage in auditory detection tasks. We tested for this form of task-related plasticity in the inferior colliculus (IC) of ferrets trained to detect a pure tone target in a sequence of noise distractors that did not overlap in time. During behavior, responses were suppressed at the target tone frequency in approximately half of IC neurons relative to the passive state. This suppression often resulted from a combination of a local tuning change and a global change in overall excitability. Local and global suppression were stronger when the target frequency was aligned to neuronal best frequency. Local suppression in the IC was indistinguishable from that described previously in auditory cortex, while global suppression was unique to the IC. The results demonstrate that engaging in an auditory task can change selectivity for task-relevant features in the midbrain, an area where these effects have not been reported previously. SIGNIFICANCE STATEMENT: Previous studies have demonstrated that the receptive fields of cortical neurons are modified when animals engage in auditory behaviors, a process that is hypothesized to provide the basis for segregating sound sources in an auditory scene. This study demonstrates for the first time that receptive fields of neurons in the midbrain inferior colliculus are also modified during behavior. The magnitude of the tuning changes is similar to previous reports in cortex. These results support a hierarchical model of behaviorally driven sound segregation that begins in the subcortical auditory network.

Smith, J. A., Kalimullah, F. A., Erickson, C. P., & Peng, L. S. (2015). Scleromyxedema secondary to hepatitis c virus and successfully treated with antiviral therapy. *Dermatology Online Journal, 21*(9)

Sonnenberg, A., Enestvedt, B. K., & Bakis, G. (2015). Management of suspected choledocholithiasis: A decision analysis for choosing the optimal imaging modality. *Digestive Diseases and Sciences,* BACKGROUND AND AIMS: Magnetic resonance cholangiography (MRC), endoscopic ultrasound (EUS), and endoscopic retrograde cholangio-pancreatography (ERCP) all represent viable options to establish the diagnosis of choledocholithiasis. The aim of the study was to assess how the three imaging modalities perform in head-to-head comparisons and in what order to apply them

when using these procedures sequentially. METHODS: A threshold analysis using a decision tree was modeled to compare the costs associated with different imaging techniques of the biliary system in a patient with suspected cholestasis secondary to choledocholithiasis. The main outcome parameter was the pre-test probability of common bile duct (CBD) stones that would guide the physician towards starting the work-up with MRC or EUS versus going straight to ERCP as the primary procedure. RESULTS: For low pre-test probabilities of CBD stones in the common bile duct, MRC represents the procedure of choice. For pre-test probabilities ranging between 40 and 91 %, EUS should be the preferred imaging modality. If CBD stones are suspected with an even higher pre-test probability, patients could go straight to ERCP as their first procedure. Low costs associated with any of the three procedures increase its range of applicability at the expense of the other competing imaging modalities. CONCLUSIONS: MRC, EUS, and ERCP should be used in sequence and dependent on the pre-test probability of choledocholithiasis.

Sonnenberg, A., & Genta, R. M. (2015). Inverse association between helicobacter pylori gastritis and microscopic colitis. *Inflammatory Bowel Diseases,*

BACKGROUND: Inflammatory bowel disease is known to be inversely associated with Helicobacter pylori infection of the upper gastrointestinal tract. We hypothesized that a similar inverse association also applied to microscopic colitis. METHODS: The associations between microscopic colitis and presence of H. pylori-positive chronic active gastritis (CAG), H. pylori-negative CAG, intestinal metaplasia, or gastric atrophy were expressed as odds ratios with their 95% confidence intervals. Multivariate logistic regression analyses were used to adjust these associations for sex, age, percentage residents per ZIP code with white, black, Hispanic, or Asian ethnicity, percentage with college education, average housing values, annual income, and population size of individual ZIP codes. RESULTS: H. pylori-positive CAG was less common among patients with than without microscopic colitis (odds ratio = 0.61; 95% confidence interval, 0.52-0.70). Intestinal metaplasia also occurred less frequently among patients with than without microscopic colitis (0.75, 0.65-0.86). These inverse associations remained unaffected by adjustments for parameters of ethnicity and socioeconomic status. In contradistinction with H. pylori-positive CAG, H. pylori-negative CAG was more common in patients with than without microscopic colitis (1.54, 1.17-1.97). CONCLUSIONS: H. pylori infection and microscopic colitis are inversely associated. This

observation is consistent with similar inverse associations found between H. pylori and inflammatory bowel disease. These relationships may provide clues about the yet unknown etiology of microscopic colitis.

Sonnenberg, A., & Genta, R. M. (2015). Prevalence of benign gastric polyps in a large pathology database. *Digestive and Liver Disease : Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, 47*(2), 164-169.

AIMS: The aim of the study was to utilize a large national histopathology database for the analysis of the clinical epidemiology of gastric polyps. METHODS: In a case-control study, 71,575 case subjects with gastric polyps were compared to 741,351 control subjects without gastric polyps. RESULTS: Of all patients, 7.72% harboured fundic gland polyps, 1.79% gastric hyperplastic polyps, 0.09% gastric adenomas, and 0.06% type I neuroendocrine tumours. All types showed a clear-cut age-dependent rise. Reflux disease was significantly more common in patients with fundic gland polyps and significantly less common in patients with gastric adenomas or neuroendocrine tumours. Anaemia was more common in patients with gastric hyperplastic polyps, gastric adenomas, or neuroendocrine tumours. Helicobacter pylori was found significantly less frequently in all subjects with gastric polyps than in controls. Intestinal metaplasia and gastric atrophy were both more common in gastric adenoma and neuroendocrine tumours and less common in fundic gland polyps than in controls. Different polyp types tended to coincide in the same patients. CONCLUSIONS: Gastric hyperplastic polyps appeared to mark the beginning of a progression from chronic gastritis to intestinal metaplasia and gastric atrophy, which leads to diminished gastric acid output and increased gastrin secretion. Gastric adenoma and neuroendocrine tumours reflect later stages of this process.

Soroceanu, A., Diebo, B. G., Burton, D., Smith, J. S., Deviren, V., Shaffrey, C., et al. (2015). Radiographical and implant-related complications in adult spinal deformity surgery: Incidence, patient risk factors, and impact on health-related quality of life. *Spine, 40*(18), 1414-1421.

Sparks, T. N., Yeaton-Massey, A., Granados, J. M., Handler, S. J., Meyer, M. R., & Caughey, A. B. (2015). Preference toward future mode of delivery: How do antepartum preferences and prior

delivery experience contribute? *Journal of Maternal-Fetal and Neonatal Medicine, 28*(14), 1673-1678.

Spear, J. M., Noble, A. J., Xie, Q., Sousa, D. R., Chapman, M. S., & Stagg, S. M. (2015). The influence of frame alignment with dose compensation on the quality of single particle reconstructions. *Journal of Structural Biology,*

As direct electron detection devices in cryo-electron microscopy become ubiquitous, the field is now ripe for new developments in image analysis techniques that take advantage of their increased SNR coupled with their high-throughput frame collection abilities. In approaching atomic resolution of native-like biomolecules, the accurate extraction of structural locations and orientations of side-chains from frames depends not only on the electron dose that a sample receives but also on the ability to accurately estimate the CTF. Here we use a new 2.8A resolution structure of a recombinant gene therapy virus, AAV-DJ with Arixtra, imaged on an FEI Titan Krios with a DE-20 direct electron detector to probe new metrics including relative side-chain density and ResLog analysis for optimizing the compensation of electron beam damage and to characterize the factors that are limiting the resolution of the reconstruction. The influence of dose compensation on the accuracy of CTF estimation and particle classifiability are also presented. We show that rigorous dose compensation allows for better particle classifiability and greater recovery of structural information from negatively charged, electron-sensitive side-chains, resulting in a more accurate macromolecular model.

Spencer, P. S., Garner, C. E., Palmer, V. S., & Kisby, G. E. (2015). *Environmental neurotoxins linked to a prototypical neurodegenerative disease*

Srinivasan, B., Baratashvili, M., van der Zwaag, M., Kanon, B., Colombelli, C., Lambrechts, R. A., et al. (2015). Extracellular 4'-phosphopantetheine is a source for intracellular coenzyme A synthesis. *Nature Chemical Biology, 11*(10), 784-792.

The metabolic cofactor coenzyme A (CoA) gained renewed attention because of its roles in neurodegeneration, protein acetylation, autophagy and signal transduction. The long-standing dogma is that eukaryotic cells obtain CoA exclusively via the uptake of extracellular precursors, especially vitamin B5, which is intracellularly converted through five conserved enzymatic

reactions into CoA. This study demonstrates an alternative mechanism that allows cells and organisms to adjust intracellular CoA levels by using exogenous CoA. Here CoA was hydrolyzed extracellularly by ectonucleotide pyrophosphatases to 4'-phosphopantetheine, a biologically stable molecule able to translocate through membranes via passive diffusion. Inside the cell, 4'-phosphopantetheine was enzymatically converted back to CoA by the bifunctional enzyme CoA synthase. Phenotypes induced by intracellular CoA deprivation were reversed when exogenous CoA was provided. Our findings answer long-standing questions in fundamental cell biology and have major implications for the understanding of CoA-related diseases and therapies.

Stevens, B., Maxson, J., Tyner, J., Smith, C. A., Gutman, J. A., Robinson, W., et al. (2015). Clonality of neutrophilia associated with plasma cell neoplasms: Report of a SETBP1 mutation and analysis of a single institution series. *Leukemia & Lymphoma,* , 1-22.

A rare but well-known association between plasma cell neoplasms and neutrophilia is known to exist. Whether the neutrophilia is secondary to the plasma cell neoplasm or this convergence represents two independent clonal disorders is unclear. We reviewed five consecutive cases from a single institution over a three-year period, applying molecular, cytogenetic and cytokine-profiling approaches to determine whether neutrophilia associated with plasma cell neoplasms represents a reactive or clonal process. We report, for the first time, the occurrence of a SETBP1 mutation in two cases, as well as changes in G-CSF and IL-6 in SETBP1 wild type vs. mutated patients that are supportive of a hypothesis that neutrophilia associated with plasma cell neoplasms may sometimes be reactive and may sometimes represent a second clonal entity. Finally, using an ex vivo drug screening platform we report the potential efficacy of the multi-kinase inhibitor dasatinib in select patients.

Tantbirojn, D., Pfeifer, C. S., Amini, A. N., & Versluis, A. (2014). Simple optical method for measuring free shrinkage. *Dental Materials,*

Tantbirojn, D., Pfeifer, C. S., Amini, A. N., & Versluis, A. (2015). Simple optical method for measuring free shrinkage. *Dental Materials : Official Publication of the Academy of Dental Materials,*

OBJECTIVES: A simple optical method for measuring polymerization shrinkage of dental composites is compared with an established dilatometer. METHODS: Five restorative composites

were used to test the methods: Filtek Supreme Ultra (3M ESPE), Filtek LS (3M ESPE), Premise (Kerr), Gradia Direct (GC), and GC Kalore (GC). Uncured composites were attached to sandblasted silane-treated glass slides. The slides were placed sample side inside a mercury-filled dilatometer (ADAF). The mercury levels were recorded as the materials were light-cured through the glass-slides (40s). Mercury levels, which correlated with volumetric shrinkage, were recorded for 60min (N=6). For the optical method, uncured composite was placed on a smooth silicone platform. A pre-polymerization image was captured under a stereomicroscope, and the specimen was light-cured (40s). Post-polymerization images were captured at 2, 10, 60, and 90min (N=10). Composite outlines were traced to obtain projected surface areas (ImageJ) and volumetric shrinkage was calculated. Results were analyzed using two-way ANOVA (alpha=0.05) and Pearson Correlation tests. Shrinkage deformation for both methods was modeled using finite element analysis. RESULTS: Volumetric shrinkage at 60min ranged between 1.24% and 2.24% for dilatometer and 1.35-2.68% for optical methods. Optical method shrinkage was consistently higher than the dilatometer (P=.0001), but the ranking of the composites was the same (Pearson Correlation Coefficient 0.9997). Finite element analysis showed that lower shrinkage values of the dilatometer method could be attributed to bonding of its samples. SIGNIFICANCE: The optical method using a general-purpose stereomicroscope and public-domain software is a simple and accurate alternative to measure free shrinkage.

Tao, L., Stich, T. A., Butterfield, C. N., Romano, C. A., Spiro, T. G., Tebo, B. M., et al. (2015). Mn(II) binding and subsequent oxidation by the multicopper oxidase MnxG investigated by electron paramagnetic resonance spectroscopy. *Journal of the American Chemical Society, 137*(33), 10563-10575.

Tereshchenko, L. G., & Josephson, M. E. (2015). Frequency content and characteristics of ventricular conduction. *Journal of Electrocardiology,*

The spectrum of frequencies producing the QRS complex has not been fully explored. In this manuscript we review previous studies of QRS frequency content, and discuss our novel method of the conjoint analysis of the ECG signal in six dimensions: in the domain of three space dimensions, in time domain, and in frequency domain. Orbital frequency of QRS loop is

introduced as a six-dimensional characteristic of ventricular conduction, which helped to reveal inapparent ventricular conduction, and to characterize electrophysiological substrate. In this paper, we review our novel method in the historical context.

Theodoroff, S. M., Lewis, M. S., Folmer, R. L., Henry, J. A., & Carlson, K. F. (2015). Hearing impairment and tinnitus: Prevalence, risk factors, and outcomes in us service members and veterans deployed to the iraq and afghanistan wars. *Epidemiologic Reviews, 37*(1), 71-85.

Tholey, D. M., & Ahn, J. (2015). Impact of hepatitis C virus infection on hepatocellular carcinoma. *Gastroenterology Clinics of North America,*

Tibayan, F. A., Louey, S., Jonker, S. S., Espinoza, H. M., Chattergoon, N. N., You, F., et al. (2015). Increased systolic load causes adverse remodeling of fetal aortic and mitral valves. *American Journal of Physiology.Regulatory, Integrative and Comparative Physiology,* , ajpregu.00040.2015. While abnormal hemodynamic forces alter fetal myocardial growth, little is known about whether such insults dysregulate fetal cardiac valve development. We hypothesized that chronically elevated systolic load would detrimentally alter fetal valve growth. Sixteen chronically instrumented fetal sheep received either a continuous infusion of adult sheep plasma to increase fetal blood pressure (n=8), or a Lactated Ringers infusion as a volume control (n=8) beginning on day 126+/-4 of gestation. After 8 days, mean arterial pressure was higher in the plasma infusion group (63.0 mm Hg vs. 41.8 mm Hg, $P < 0.01$). Mitral annular septal-lateral diameter (11.9 mm vs. 9.1 mm, $P < 0.05$), anterior leaflet length (7.7mm vs. 6.4 mm, $P < 0.05$), and posterior leaflet length (4.0 mm vs. 3.0 mm, $P < 0.05$) were greater in the elevated load group. mRNA levels of Notch-1, TGF-beta2, Wnt-2b, BMP-1, and versican were suppressed in aortic and mitral valve leaflets; elastin and alpha-1 type I collagen mRNA levels were suppressed in the aortic valves only. We conclude that sustained elevated pressure load on the fetal heart valve leads to anatomic remodeling and, surprisingly, suppression of signaling and extracellular matrix genes that are important to valve development. These novel findings have important implications on the developmental origins of valve disease and may have long term consequences on valve function and durability.

Trivedi, R., Gerrity, M., Rumsfeld, J. S., Spertus, J. A., Sun, H., McDonell, M., et al. (2015). Angina symptom burden associated with depression status among veterans with ischemic heart disease. *Annals of Behavioral Medicine, 49*(1), 58-65.

Trudell, A. S., Louis, J. M., Tuuli, M. G., Caughey, A. B., Odibo, A. O., & Cahill, A. G. (2015). Use of a simple clinical tool for airway assessment to predict adverse pregnancy outcomes. *American Journal of Perinatology, 32*(3), 257-262.

Tuck, K. K., Zive, D. M., Schmidt, T. A., Carter, J., Nutt, J., & Fromme, E. K. (2015). Life-sustaining treatment orders, location of death and co-morbid conditions in decedents with parkinson's disease. *Parkinsonism & Related Disorders, 21*(10), 1205-1209.
INTRODUCTION: End-of-life care in Parkinson's Disease (PD) is poorly described. Physician Orders for Life Sustaining Treatment (POLST) forms specify how much life-sustaining treatment to provide. This study aims to better understand end-of-life care in PD using data from the Oregon POLST and Death Registries. METHODS: Oregon death certificates from the years 2010-2011 were analyzed. Death certificates were matched with forms in the Oregon POLST Registry. Descriptive analyses were performed for both the full PD dataset as well as those with POLST forms. RESULTS: There were 1073 (1.8%) decedents with PD listed as a cause of death and 56,961 without. Three hundred and seventy three (35%) decedents with PD had a POLST form. POLST preferences were not significantly different between those with or without PD, however location of death was; hospital (13% PD vs 24% without $p < 0.01$), home (32% vs 40% $p < 0.01$) and care facility (52% vs 29% $p < 0.01$). Compared to those without a POLST or those without a Comfort Measures Only (CMO) order, decedents with PD and a CMO order were less likely to die in a hospital (5.4% vs 14.7% $p < 0.01$) and more likely to die at home (39.1% vs 29.1% $p < 0.01$). In those with PD, dementia was the most common comorbid condition listed on death certificates (16%). CONCLUSION: Decedents with PD die less frequently at home than the general population. POLST forms mitigate some of this discrepancy. While not often thought to be terminal, PD and its complications are commonly recorded causes of death.

Turner, K. O., Genta, R. M., & Sonnenberg, A. (2015). Oesophageal signet ring cell carcinoma as complication of gastro-oesophageal reflux disease. *Alimentary Pharmacology & Therapeutics,*

BACKGROUND: Signet ring cell carcinoma occurs as a histological variant of oesophageal adenocarcinoma. AIM: In a cross-sectional study, to pursue the hypothesis that oesophageal signet ring cell cancers constitute a complication of gastro-oesophageal reflux disease. METHODS: In a large national database of histopathology records, we accumulated 91 802 patients with Barrett's oesophagus (BE), 2817 with oesophageal nonsignet ring adenocarcinoma (EAC) and 278 with oesophageal signet ring cell carcinoma (SRC). The three groups were compared with respect to their clinical and demographic characteristics, as well as socio-economic risk factors (associated with patients' place of residence). RESULTS: About 9% of all oesophageal adenocarcinomas harboured features of signet ring cell carcinoma. Patients with oesophageal adenocarcinoma and signet ring cell carcinoma were characterised by almost identical epidemiological patterns. Patients with either cancer type were slightly older than those with Barrett's oesophagus (EAC 68.0, SRC 66.7 vs. BE 63.7 years), and both showed a striking male predominance (EAC and SRC 85% vs. BE 67%). Both cancer types were associated with a similar set of alarm symptoms, such as dysphagia, pain and weight loss. The distribution by race (Whites vs. Blacks) and socio-economic parameters, such as levels of college education and family income, were similar among the three groups of patients. CONCLUSIONS: Signet ring cell carcinoma is a rare variant of oesophageal adenocarcinoma with similar epidemiological characteristics. The reasons why a minority of reflux patients progress to develop signet ring cell carcinoma, rather than the usual type of oesophageal adenocarcinoma, remain unknown.

Tuuli, M. G., Odibo, A. O., Caughey, A. B., Roehl, K., Macones, G. A., & Cahill, A. G. (2015). Are there differences in the first stage of labor between black and white women? *American Journal of Perinatology, 32*(3), 233-237.

Tynan, M. A., Morris, D., & Weston, T. (2015). Continued implications of taxing roll-your-own tobacco as pipe tobacco in the USA. *Tobacco Control, 24*(E2), e125-e127.

Vallejo, M. C., & Mayinger, P. (2015). Delayed turnover of unphosphorylated Ssk1 during carbon stress activates the yeast Hog1 map kinase pathway. *PloS One, 10*(9), e0137199.
In Saccharomyces cerevisiae, the Hog1 mitogen-activated protein kinase (MAPK) pathway coordinates the adaptation to osmotic stress and was recently reported to respond to acute

changes in glucose levels. Similarly as in osmotic stress, glucose starvation leads to a transient accumulation of Hog1 in the nucleus. However, the kinetics and the mechanism of Hog1 activation are different for these stress conditions. During osmotic shock the activation of Hog1 can be transduced by either the Sho1 or the Sln1/Ypd1/Ssk1 branch. During glucose starvation the phosphorylation of Hog1 is slower and is completely dependent on Ssk1, but independent of Sho1. To characterize the mechanism of activation of Hog1 during carbon stress, we examined the turnover of Ssk1 protein levels upon glucose starvation in the presence of cycloheximide and monitored protein levels by western blotting. Our data demonstrate that unphosphorylated Ssk1 was quickly degraded during exponential growth and after osmotic stress but remained remarkably stable during glucose limitation. We conclude that glucose starvation induces a delay in the turnover of unphosphorylated Ssk1, which is sufficient to activate the Hog1 MAPK pathway. Although unphosphorylated Ssk1 is known to be degraded by the proteasome, its stabilization is apparently not due to changes in cellular localization or decrease in ubiquitination levels during glucose limitation.

Vanner, E. A., & Mansberger, S. L. (2015). Putting the "metal" back in meta-analysis. *American Journal of Ophthalmology,*

Varner, M. W., Marshall, N. E., Rouse, D. J., Jablonski, K. A., Leveno, K. J., Reddy, U. M., et al. (2015). The association of cord serum cytokines with neurodevelopmental outcomes. *American Journal of Perinatology, 30*(2), 115-122.

OBJECTIVE: To test whether elevated umbilical cord serum inflammatory cytokine levels predicted subsequent cerebral palsy (CP) or neurodevelopmental delay (NDD). STUDY DESIGN: Nested case-control analysis within a clinical trial of antenatal magnesium sulfate (MgSO4) before anticipated preterm birth (PTB) for prevention of CP, with evaluation of surviving children at the age of 2. NDD was defined as a Bayley psychomotor developmental index (PDI) and/or mental developmental index (MDI) /= 85, were matched by race and gestational age. Cord serum was analyzed for interleukin-8 (IL-8) interleukin-1 beta (IL-1beta), and tumor necrosis factor-alpha (TNF-alpha) levels. Elevated cytokine levels were defined as >/= 75th percentile in placebo-exposed controls. Analyses compared case/control cytokine levels, adjusting for MgSO4

exposure, gestational age, race/ethnicity, and sociodemographic differences. RESULTS: Logistic regression analysis with 339 cases and 276 controls showed that elevated IL-8 and IL-1beta were more common in cord blood serum from infants with subsequent low MDI as compared with controls. After adjusting for additional confounders, the significant differences were no longer evident. Cytokine levels (IL-8, IL-1beta, and TNF-alpha) were not elevated with CP or low PDI. CONCLUSION: Cord serum IL-8, IL-1beta, and TNF-alpha levels in preterm infants are not associated with subsequent CP or NDD.

Veltri, L. M. (2015). Obstetrical staff nurses experiences of clinical learning. *Nurse Education in Practice, 15*(1), 44-51.

The clinical learning experience is used in nursing programs of study worldwide to prepare nurses for professional practice. This study's purpose was to use Naturalistic Inquiry to understand the experiences of staff nurses in an obstetrical unit with undergraduate nursing students present for clinical learning. A convenience sample of 12 staff nurses, employed on a Family Birth Center, participated in semi-structured interviews. The constant comparative method as modified by Lincoln and Guba was used to analyze data. Five themes related to staff nurses experiences of clinical learning were identified: Giving and Receiving; Advancing Professionally and Personally; Balancing Act; Getting to Know and Working with You; and Past and Present. This research highlights staff nurses' experiences of clinical learning in undergraduate nursing education. Staff nurses exert a powerful, long lasting influence on students. A need exists to prepare and judiciously select nurses to work with students. Clinical agencies and universities can take joint responsibility providing tangible incentives, financial compensation, and recognition to all nurses working with nursing students.

Ventres, W. B., & Frankel, R. M. (2015). Shared presence in physician-patient communication: A graphic representation. *Families, Systems and Health, 33*(3), 270-279.

Vetto, J. T. (2015). Reflections: Cancer education and "the platinum rule". *Journal of Cancer Education : The Official Journal of the American Association for Cancer Education,*

Vidula, H., Liu, K., Criqui, M. H., Szklo, M., Allison, M., Sibley, C., et al. (2015). Metabolic syndrome and incident peripheral artery disease - the multi-ethnic study of atherosclerosis. *Atherosclerosis, 243*(1), 198-203.

OBJECTIVE: We evaluated whether metabolic syndrome (MetS) is associated with an increased incidence of lower extremity peripheral artery disease (PAD) in community dwelling people free of clinical cardiovascular disease at baseline. We assessed whether higher levels of inflammatory biomarkers may mediate the association of MetS with incident PAD. METHODS: MetS was defined at baseline as the presence of three or more of the following components: elevated waist circumference, triglycerides >/=150 mg/dL, reduced high-density lipoprotein (HDL) cholesterol, blood pressure >/=130/85 mm Hg or taking blood pressure medication, and fasting glucose >/=100 mg/dL and /=0.15 or medical record confirmed PAD outcome. Multivariable Poisson regression was used to estimate the association between MetS and incident PAD. RESULTS: Among 4817 participants without PAD at baseline, 1382 (29%) had MetS. Adjusting for age, sex, race, smoking, physical activity, low-density lipoprotein cholesterol, baseline ABI, and other confounders, 23/1382 (1.7%) people with MetS developed PAD vs. 30/3435 (0.87%) people without MetS (risk ratio = 1.78 [95% Confidence Interval (CI), 1.04 to 2.82], P = 0.031). Adjusting for C-reactive protein, fibrinogen, or interleukin-6 did not attenuate this association. CONCLUSION: People free of clinical cardiovascular disease with MetS are at increased risk for PAD. Our findings suggest that this association is not mediated by inflammation.

Vinet, E., Pineau, C. A., Clarke, A. E., Scott, S., Fombonne, E., Joseph, L., et al. (2015). Increased risk of autism spectrum disorders in children born to women with systemic lupus erythematosus: Results from the OSLER cohort. *Arthritis & Rheumatology (Hoboken, N.J.),*

OBJECTIVE: In utero exposure to maternal antibodies and cytokines are potential risk factors for autism spectrum disorders (ASD). We aimed to determine if children born to mothers with systemic lupus erythematosus (SLE) have an increased risk of ASD compared to children born to mothers without SLE. METHODS: The "Offspring of SLE mothers Registry (OSLER)" is a large population-based cohort, identified through Quebec's healthcare databases (1989-2009), including all women who had >/=1 hospitalization for delivery after SLE diagnosis, and a randomly selected control group of women, matched >/=4:1 for age and year of delivery. We

identified children born live to SLE mothers and their matched controls, and ascertained ASD, performing multivariate analyses to adjust for parental demographics, sex and birth order of child, maternal comorbidities, and obstetrical complications. RESULTS: 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Children born to women with SLE had more ASD compared to controls [1.4% (95%CI 0.8,2.5) versus 0.6% (95%CI 0.5,0.8), difference 0.8% (95%CI 0.1,1.9)]. Mean age at ASD diagnosis was younger in offspring of SLE mothers (3.8 years, 95%CI 1.8,5.8) as opposed to controls (5.7 years, 95%CI 4.9,6.5). In primary multivariate analysis, SLE offspring had substantially increased risk of ASD versus controls (OR 2.19, 95%CI 1.09,4.39). CONCLUSIONS: Compared to children from the general population, children born to women with SLE have an increased risk of ASD, although in absolute terms it represents a rare outcome. These hypothesis-generating data provide direction for additional studies of maternal autoimmunity and ASD risk. This article is protected by copyright. All rights reserved.

Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., et al. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the global burden of disease study 2013. *The Lancet, 386*(9995), 743-800.

Vugia, D. J., Meek, J. I., Danila, R. N., Jones, T. F., Schaffner, W., Baumbach, J., et al. (2015). Training in infectious disease epidemiology through the emerging infections program sites. *Emerging Infectious Diseases, 21*(9), 1516-1519.

Wallace, N. T., Cohen, D. J., Gunn, R., Beck, A., Melek, S., Bechtold, D., et al. (2015). Start-up and ongoing practice expenses of behavioral health and primary care integration interventions in the advancing care together (ACT) program. *Journal of the American Board of Family Medicine : JABFM, 28 Suppl 1*, S86-97.

PURPOSE: Provide credible estimates of the start-up and ongoing effort and incremental practice expenses for the Advancing Care Together (ACT) behavioral health and primary care integration interventions. METHODS: Expenditure data were collected from 10 practice intervention sites using an instrument with a standardized general format that could accommodate the unique

elements of each intervention. RESULTS: Average start-up effort expenses were $44,076 and monthly ongoing effort expenses per patient were $40.39. Incremental expenses averaged $20,788 for start-up and $4.58 per patient for monthly ongoing activities. Variations in expenditures across practices reflect the differences in intervention specifics and organizational settings. Differences in effort to incremental expenditures reflect the extensive use of existing resources in implementing the interventions. CONCLUSIONS: ACT program incremental expenses suggest that widespread adoption would likely have a relatively modest effect on overall health systems expenditures. Practice effort expenses are not trivial and may pose barriers to adoption. Payers and purchasers interested in attaining widespread adoption of integrated care must consider external support to practices that accounts for both incremental and effort expense levels. Existing knowledge transfer mechanisms should be employed to minimize developmental start-up expenses and payment reform focused toward value-based, Triple Aim-oriented reimbursement and purchasing mechanisms are likely needed.

Ward, M. M., Deodhar, A., Akl, E. A., Lui, A., Ermann, J., Gensler, L. S., et al. (2015). American college of Rheumatology/Spondylitis association of America/Spondyloarthritis research and treatment network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Care & Research,*

OBJECTIVE: To provide evidence-based recommendations for the treatment of patients with ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA). METHODS: A core group led the development of the recommendations, starting with the treatment questions. A literature review group conducted systematic literature reviews of studies that addressed 57 specific treatment questions, based on searches conducted in OVID Medline (1946-2014), PubMed (1966-2014), and the Cochrane Library. We assessed the quality of evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method. A separate voting group reviewed the evidence and voted on recommendations for each question using the GRADE framework. RESULTS: In patients with active AS, the strong recommendations included use of nonsteroidal antiinflammatory drugs (NSAIDs), use of tumor necrosis factor inhibitors (TNFi) when activity persists despite NSAID treatment, not to use systemic glucocorticoids, use of physical therapy, and use of hip arthroplasty for patients with advanced

hip arthritis. Among the conditional recommendations was that no particular TNFi was preferred except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom TNFi monoclonal antibodies should be used. In patients with active nonradiographic axial SpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi. Other recommendations for patients with nonradiographic axial SpA were based on indirect evidence and were the same as for patients with AS. CONCLUSION: These recommendations provide guidance for the management of common clinical questions in AS and nonradiographic axial SpA. Additional research on optimal medication management over time, disease monitoring, and preventive care is needed to help establish best practices in these areas.

Weddle, M., Empey, A., Crossen, E., Green, A., Green, J., & Phillipi, C. A. (2015). Are pediatricians complicit in vitamin K deficiency bleeding? *Pediatrics,*

The American Academy of Pediatrics recommends that all newborns receive a single dose of intramuscular vitamin K to prevent vitamin K deficiency bleeding. How should the clinician respond when parents decline vitamin K? Although vitamin K deficiency bleeding can have devastating sequelae, they are uncommon; therefore, parents are generally allowed to decline vitamin K after counseling is provided. When parents ask for a vitamin K preparation of unproven effectiveness, should the clinician honor that request? To address these questions, we present a case of a healthy newborn whose parents declined intramuscular vitamin K and requested an oral preparation. Two general pediatricians discuss the medical and ethical issues these situations pose, and the parents describe their experience.

Weiss, S. L., Fitzgerald, J. C., Maffei, F. A., Kane, J. M., Rodriguez-Nunez, A., Hsing, D. D., et al. (2015). Discordant identification of pediatric severe sepsis by research and clinical definitions in the SPROUT international point prevalence study. *Critical Care, 19*(1)

Werner, R. N., Stockfleth, E., Connolly, S. M., Correia, O., Erdmann, R., Foley, P., et al. (2015). Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis - international league of dermatological societies in cooperation with the european dermatology forum - short version. *Journal of the European Academy of Dermatology and Venereology : JEADV,*

BACKGROUND: Actinic keratosis (AK) is a frequent health condition attributable to chronic exposure to ultraviolet radiation. Several treatment options are available and evidence based guidelines are missing. OBJECTIVES: The goal of these evidence- and consensus-based guidelines was the development of treatment recommendations appropriate for different subgroups of patients presenting with AK. A secondary aim of these guidelines was the implementation of knowledge relating to the clinical background of AK, including consensus-based recommendations for the histopathological definition, diagnosis and the assessment of patients. METHODS: The guidelines development followed a pre-defined and structured process. For the underlying systematic literature review of interventions for AK, the methodology suggested by the Cochrane Handbook for Systematic Reviews of Interventions, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was adapted. All recommendations were consented during a consensus conference using a formal consensus methodology. Strength of recommendations was expressed based on the GRADE approach. If expert opinion without external evidence was incorporated into the reasoning for making a certain recommendation, the rationale was provided. The Guidelines underwent open public review and approval by the commissioning societies. RESULTS: Various interventions for the treatment of AK have been assessed for their efficacy. The consenting procedure led to a treatment algorithm as shown in the guidelines document. Based on expert consensus, the present guidelines present recommendations on the classification of patients, diagnosis and histopathological definition of AK. Details on the methods and results of the systematic literature review and guideline development process have been published separately. CONCLUSIONS: International guidelines are intended to be adapted to national or regional circumstances (regulatory approval, availability and reimbursement of treatments).

Wieghard, N. E., Hart, K. D., Herzig, D. O., Lu, K. C., & Tsikitis, V. L. (2015). Psychiatric illness is a disparity in the surgical management of rectal cancer. *Annals of Surgical Oncology,*

BACKGROUND: Psychiatric disorders are common in the US and represent a major health disparity but little is known about their impact on surgical management and outcomes in cancer. OBJECTIVE: The aim of this study was to determine whether rectal cancer patients with

psychiatric diagnoses have fewer sphincter-preserving procedures and higher postoperative complications. METHODS: Overall, 23,914 patients from the Nationwide Inpatient Sample (NIS) who underwent surgery for rectal cancer from 2004 to 2011 were identified. Patients with comorbid common psychiatric diagnoses were identified by International Classification of Diseases, Ninth Revision (ICD-9) codes. Main outcomes were measured by operation performed, length of stay (LOS), postoperative complications, and discharge disposition. RESULTS: Twenty percent of patients had a psychiatric diagnosis, with substance use being the most common psychiatric disorder (63 %). Patients with psychiatric diagnoses were more likely to be younger, White, have lower income, and have Medicaid insurance ($p < 0.001$) than those without. In a logistic regression model, patients with any psychiatric diagnosis were less likely to have sphincter-sparing surgery, controlling for patient sociodemographics, Charlson score, hospital procedure volume, and year (odds ratio 0.77; 95 % CI 0.72-0.83). LOS and postoperative complications were similar among the cohorts. Patients with psychiatric disorders were more likely to have home health care at discharge ($p < 0.001$). CONCLUSIONS: Fewer sphincter-sparing procedures were performed on rectal cancer patients with psychiatric diagnoses. However, no significant differences in postoperative complications were observed.

Windschuttl, S., Kampfer, C., Mayer, C., Flenkenthaler, F., Frohlich, T., Schwarzer, J. U., et al. (2015). Human testicular peritubular cells secrete pigment epithelium-derived factor (PEDF), which may be responsible for the avascularity of the seminiferous tubules. *Scientific Reports, 5*, 12820. Male fertility depends on spermatogenesis, which takes place in the seminiferous tubules of the testis. This compartment is devoid of blood vessels, which are however found in the wall of the seminiferous tubules. Our proteomic study using cultured human testicular peritubular cells (HTPCs) i.e. the cells, which form this wall, revealed that they constitutively secrete pigment epithelium-derived factor, PEDF, which is known to exert anti-angiogenic actions. Immunohistochemistry supports its presence in vivo, in the human tubular wall. Co-culture studies and analysis of cell migration patterns showed that human endothelial cells (HUVECs) are repulsed by HTPCs. The factor involved is likely PEDF, as a PEDF-antiserum blocked the repulsing action. Thus testicular peritubular cells, via PEDF, may prevent vascularization of human seminiferous tubules. Dihydrotestosterone (DHT) increased PEDF (qPCR) in HTPCs, however PEDF

expression in the testis of a non-human primate occurs before puberty. Thus PEDF could be involved in the establishment of the avascular nature of seminiferous tubules and after puberty androgens may further reinforce this feature. Testicular microvessels and blood flow are known to contribute to the spermatogonial stem cell niche. Hence HTPCs via control of testicular microvessels may contribute to the regulation of spermatogonial stem cells, as well.

Winthrop, K. L., Novosad, S. A., Baddley, J. W., Calabrese, L., Chiller, T., Polgreen, P., et al. (2015). Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: Consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Annals of the Rheumatic Diseases,*

No consensus has previously been formed regarding the types and presentations of infectious pathogens to be considered as 'opportunistic infections' (OIs) within the setting of biologic therapy. We systematically reviewed published literature reporting OIs in the setting of biologic therapy for inflammatory diseases. The review sought to describe the OI definitions used within these studies and the types of OIs reported. These findings informed a consensus committee (infectious diseases and rheumatology specialists) in deliberations regarding the development of a candidate list of infections that should be considered as OIs in the setting of biologic therapy. We reviewed 368 clinical trials (randomised controlled/long-term extension), 195 observational studies and numerous case reports/series. Only 11 observational studies defined OIs within their methods; no consistent OI definition was identified across studies. Across all study formats, the most numerous OIs reported were granulomatous infections. The consensus group developed a working definition for OIs as 'indicator' infections, defined as specific pathogens or presentations of pathogens that 'indicate' the likelihood of an alteration in host immunity in the setting of biologic therapy. Using this framework, consensus was reached upon a list of OIs and case-definitions for their reporting during clinical trials and other studies. Prior studies of OIs in the setting of biologic therapy have used inconsistent definitions. The consensus committee reached agreement upon an OI definition, developed case definitions for reporting of each pathogen, and recommended these be used in future studies to facilitate comparison of infection risk between biologic therapies.

Winthrop, K. L., Park, S. H., Gul, A., Cardiel, M. H., Gomez-Reino, J. J., Tanaka, Y., et al. (2015). Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases,*

OBJECTIVES: To evaluate the risk of opportunistic infections (OIs) in patients with rheumatoid arthritis (RA) treated with tofacitinib. METHODS: Phase II, III and long-term extension clinical trial data (April 2013 data-cut) from the tofacitinib RA programme were reviewed. OIs defined a priori included mycobacterial and fungal infections, multidermatomal herpes zoster and other viral infections associated with immunosuppression. For OIs, we calculated crude incidence rates (IRs; per 100 patient-years (95% CI)); for tuberculosis (TB) specifically, we calculated rates stratified by patient enrolment region according to background TB IR (per 100 patient-years): low (0.01 to 0.05). RESULTS: We identified 60 OIs among 5671 subjects; all occurred among tofacitinib-treated patients. TB (crude IR 0.21, 95% CI of (0.14 to 0.30)) was the most common OI (n=26); median time between drug start and diagnosis was 64 weeks (range 15-161 weeks). Twenty-one cases (81%) occurred in countries with high background TB IR, and the rate varied with regional background TB IR: low 0.02 (0.003 to 0.15), medium 0.08 (0.03 to 0.21) and high 0.75 (0.49 to 1.15). In Phase III studies, 263 patients diagnosed with latent TB infection were treated with isoniazid and tofacitinib concurrently; none developed TB. For OIs other than TB, 34 events were reported (crude IR 0.25 (95% CI 0.18 to 0.36)). CONCLUSIONS: Within the global tofacitinib RA development programme, TB was the most common OI reported but was rare in regions of low and medium TB incidence. Patients who screen positive for latent TB can be treated with isoniazid during tofacitinib therapy.

Wong, C. K., Young, R. S., Ow-Wing, C., & Karimi, P. (2015). Determining 1-yr prosthetic use for mobility prognoses for community-dwelling adults with lower-limb amputation: Development of a clinical prediction rule. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists,*

OBJECTIVE: The objective of this study was to develop a prognostic clinical prediction rule to identify people not achieving community walking level prosthetic use after 1 yr. DESIGN: This is a prospective longitudinal cohort study of community-dwelling adults with lower-limb amputations recruited from support groups and prosthetic clinics. Participants completed

Activities-specific Balance Confidence and Houghton prosthetic use for mobility self-report scales and the Berg Balance Scale. The clinical prediction rule was developed using multivariate logistic regression, receiver operating curves, and probability statistics to identify people not achieving community walking level prosthetic use (Houghton scores 0.96) using four criteria: initial Houghton, Activities-specific Balance Confidence, and Berg Balance Scale tasks 9 (retrieve object from floor) and 10 (look behind over shoulders). Failure to exceed cutoff scores in two or more criteria yielded posttest probability of not reaching community walking prosthetic use 1 yr later for 90% of participants or higher. CONCLUSIONS: Accurate 1-yr prosthetic use for mobility prognoses can be obtained by screening prosthetic use, balance confidence, and balance ability to identify community-dwelling people with lower-limb amputations unlikely to achieve community walking prosthetic use.

Wood, A. M., Frey, H. A., Tuuli, M. G., Caughey, A. B., Odibo, A. O., Macones, G. A., et al. (2015). Optimal admission cervical dilation in spontaneously laboring women. *American Journal of Perinatology,*

Objective To estimate the impact of admission cervical dilation on the risk of cesarean in spontaneously laboring women at term. Study Design Secondary analysis of a prospective cohort study of women admitted in term labor with a singleton gestation. Women with rupture of membranes before admission, induction of labor, or prelabor cesarean were excluded. The association between cesarean and cervical dilation at admission was estimated, and results were stratified by parity. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated, using cervical dilation >/= 6 cm as the reference group. Cesarean for arrest was secondarily explored. Results A total of 2,033 spontaneously laboring women met inclusion criteria. Women admitted at /=6 cm (13.2 vs. 3.5%; RR 3.73; 95% CI 1.94-7.17). The increased risk was noted in nulliparous (16.8 vs. 7.1%; RR 2.35; 95% CI 0.90-6.13) and multiparous (11.0 vs. 2.5%; RR 4.36; 95% CI 1.80-10.52) women, but was statistically significant only in multiparous women. Conclusions Decreasing cervical dilation at admission, particularly <6 cm, is a modifiable risk factor for cesarean, especially in multiparous women. This should be considered in the decision-making process about timing of admission in term labor.

Wood, P. L., Medicherla, S., Sheikh, N., Terry, B., Phillipps, A., Kaye, J. A., et al. (2015). Targeted lipidomics of fontal cortex and plasma diacylglycerols (DAG) in mild cognitive impairment and alzheimer's disease: Validation of DAG accumulation early in the pathophysiology of alzheimer's disease. *Journal of Alzheimer's Disease : JAD, 48*(2), 537-546.

Previous studies have demonstrated augmented levels of diacylglycerols (DAG) in the frontal cortex and plasma of Alzheimer's disease (AD) patients. We extended these findings from non-targeted lipidomics studies to design a lipidomics platform to interrogate DAGs and monoacylglycerols (MAG) in the frontal cortex and plasma of MCI subjects. Control subjects included both aged normal controls and controls with normal cognition, but AD pathology at autopsy, individuals termed non-demented AD neuropathology. DAGs with saturated, unsaturated, and polyunsaturated fatty acid substituents were found to be elevated in MCI frontal cortex and plasma. Tandem mass spectrometry of the DAGs did not reveal any differences in the distributions of the fatty acid substitutions between MCI and control subjects. While triacylglycerols were not altered in MCI subjects there were increases in MAG levels both in the frontal cortex and plasma. In toto, increased levels of DAGs and MAGs appear to occur early in AD pathophysiology and require both further validation in a larger patient cohort and elucidation of the lipidomics alteration(s) that lead to the accumulation of DAGs in MCI subjects.

Worth, P. J., Kunio, N. R., Siegfried, I., Sheppard, B. C., & Gilbert, E. W. (2015). Characteristics predicting clinical improvement and cure following laparoscopic adrenalectomy for primary aldosteronism in a large cohort. *American Journal of Surgery, 210*(4), 702-709.

BACKGROUND: Surgical resection is the standard of care for unilateral adrenal adenomas and hyperplasia resulting in primary aldosteronism (PA). Resolution of PA following surgery is variable and some patients continue to require some or all of their antihypertensives. Prior studies have investigated factors contributing to "cure" of PA (defined as no hypertension [HTN] medications required postoperatively). These models are a tool in patient selection, yet fail to consider the benefit of some reduction in medications, resolution of hypokalemia, or reduction in blood pressure which may improve long-term cardiovascular and renal outcomes. We sought to investigate factors contributing to postoperative improvement or complete resolution following surgery. METHODS: This is a retrospective review of prospectively collected data on 58

adrenalectomies performed for PA from December 1999 to April 2013 at a single center. Patient demographics, PA characteristics, labs, and imaging studies were evaluated, as well as operative characteristics. Mean systolic and diastolic blood pressures were calculated over several visits after discharge, and postoperative antihypertensive regimen was recorded. Patients were stratified by cured vs not cured and then again by improved vs not improved based on differences in pre- and postoperative values. Aldosteronoma Resolution Score was also calculated for each patient. RESULTS: Median age was 52.6 years, with 44.8% women and an average duration of HTN of 13.5 years. Average body mass index (BMI) was 31.5 kg/m(2); 74% of the lesions were adenomas. Patients with complications had higher BMIs than those without (36.9 vs 28.7 kg/m(2), P = .02). In comparing improved (n = 42, 72%) vs not improved (n = 16, 28%) patients, preoperative systolic blood pressure (147.5 vs 159.7 mm Hg, P = .047) and serum creatinine (.94 vs 1.32 mg/dL, P = .016) were higher in the not improved group. Cured (n = 13) vs not cured (n = 45) patients differed in terms of BMI (27.4 vs 32.7, P = .009), duration of HTN (9.1 vs 14.9 years, P = .020), and number of preoperative antihypertensives (2.1 vs 3.7, P = .002). Aldosteronoma Resolution Score was significantly higher in cured patients (3.2 vs 1.0, P < .01). CONCLUSIONS: A significant number of patients who are not cured by adrenalectomy for PA will still benefit from surgery. Obesity, duration of HTN, and number of medications may predict cure, yet fail to detect a population of patients with overall improvement. Attention to serum creatinine may help in distinguishing this population of patients.

Wright, A., Sittig, D. F., Ash, J. S., Erickson, J. L., Hickman, T. T., Paterno, M., et al. (2015). Lessons learned from implementing service-oriented clinical decision support at four sites: A qualitative study. *International Journal of Medical Informatics,*

OBJECTIVE: To identify challenges, lessons learned and best practices for service-oriented clinical decision support, based on the results of the Clinical Decision Support Consortium, a multi-site study which developed, implemented and evaluated clinical decision support services in a diverse range of electronic health records. METHODS: Ethnographic investigation using the rapid assessment process, a procedure for agile qualitative data collection and analysis, including clinical observation, system demonstrations and analysis and 91 interviews. RESULTS: We identified challenges and lessons learned in eight dimensions: (1) hardware and software

computing infrastructure, (2) clinical content, (3) human-computer interface, (4) people, (5) workflow and communication, (6) internal organizational policies, procedures, environment and culture, (7) external rules, regulations, and pressures and (8) system measurement and monitoring. Key challenges included performance issues (particularly related to data retrieval), differences in terminologies used across sites, workflow variability and the need for a legal framework. DISCUSSION: Based on the challenges and lessons learned, we identified eight best practices for developers and implementers of service-oriented clinical decision support: (1) optimize performance, or make asynchronous calls, (2) be liberal in what you accept (particularly for terminology), (3) foster clinical transparency, (4) develop a legal framework, (5) support a flexible front-end, (6) dedicate human resources, (7) support peer-to-peer communication, (8) improve standards. CONCLUSION: The Clinical Decision Support Consortium successfully developed a clinical decision support service and implemented it in four different electronic health records and four diverse clinical sites; however, the process was arduous. The lessons identified by the Consortium may be useful for other developers and implementers of clinical decision support services.

Wu, W. -., & Edelman, A. (2015). Contraceptive method initiation. using the centers for disease control and prevention selected practice guidelines. *Obstetrics and Gynecology Clinics of North America,*

Yang, R., Bentley, M., Huang, C. -., & Banker, G. (2015). *Analyzing kinesin motor domain translocation in cultured hippocampal neurons*

Yun, H., Xie, F., Delzell, E., Levitan, E. B., Chen, L., Lewis, J. D., et al. (2015). Comparative risk of hospitalized infection associated with biological agents among medicare rheumatoid arthritis patients. *Arthritis & Rheumatology (Hoboken, N.J.),*

BACKGROUND: The risks of hospitalized infection associated with biologics used to treat rheumatoid arthritis (RA) are unclear. We compared risks of hospitalized infections associated with biologics used for RA. METHODS: Using Medicare data from 2006-2011 for 100% RA patients, this retrospective cohort study identified new treatment episodes of etanercept, adalimumab, certolizumab, golimumab, infliximab, abatacept, rituximab and tocilizumab. Patients

were required to have used another biologic previously and have been continuously enrolled in Medicare medical and pharmacy plans during baseline and throughout follow up. Follow up started from the initiation date of the new biologic treatment, after previous treatment with a different biologic, and ended at the earliest date of: hospitalized infection, 12 months, > 30 days exposure gap, death, or loss of Medicare coverage. Cox regression was used to calculate the adjusted hazard ratio of hospitalized infection adjusting for an infection risk score and other confounders. RESULTS: Of 31,801 new biologic treatment episodes where patients previously used another biologic, 12.0% were with etanercept, 15.2% adalimumab, 5.9% certolizumab, 4.4% golimumab, 12.4% infliximab, 28.9% abatacept, 14.8% rituximab and 6.3% tocilizumab. During follow-up, we identified 2,530 hospitalized infections; incidence rates ranged from 13.1 (abatacept) to 18.7 (rituximab) per 100 person years. After adjustment, etanercept (HR=1.24 95% CI: 1.07-1.45), infliximab (HR=1.39 CI: 1.21-1.60) and rituximab (HR=1.36 CI: 1.21-1.53) had significantly higher hazard ratios of hospitalized infection compared to abatacept. CONCLUSION: Among RA patients with prior biologic exposure, etanercept, infliximab and rituximab were associated with a greater one year risk of hospitalized infection compared to abatacept. This article is protected by copyright. All rights reserved.

Zaninotto, G., & Hunter, J. G. (2015). Dysplastic barrett's esophagus. *World Journal of Surgery, 39*(3), 557-558.

Zerbe, K. (2015). Psychodynamic issues in the treatment of binge eating: Working with shame, secrets, no-entry, and false body defenses. *Clinical Social Work Journal,*

Zhang, C., Liu, L., Tang, M., Li, Y., Chamberlain, W., & Huang, D. (2015). Laboratory evaluation of femtosecond laser lamellar cuts in gamma-irradiated corneas. *Cornea,*
PURPOSE: To evaluate the stromal interface quality after femtosecond laser full lamellar cuts in gamma-irradiated corneas (VisionGraft sterile cornea) and to determine the limits of the cut depth using the VisionGraft as donor corneas for laser-assisted lamellar anterior keratoplasty. METHODS: Fourteen VisionGraft corneas underwent full lamellar cuts using the femtosecond laser. The percent cut depth was 17% to 21% (100 mum, n = 2), 31% to 35% (n = 3), 38% to 40% (n = 3), 45% to 48% (n = 3), and 50% (n = 3) of the total stromal thickness (not including

the epithelium). The cap and stromal bed surfaces were imaged with a scanning electron microscope. The quality of cut surfaces was graded by 2 masked observers based on two indices: ridge and roughness. Ridge grading indicated macroscopic irregularity. Roughness grading indicated microscopic irregularity. The grading was done on a subjective integer scale of 1 to 5 (1 = best and 5 = worst), which was used in a previous study of cut quality in fresh corneas. RESULTS: The ridge grading ranged from 1.5 for the shallowest cut to 2.2 for the deepest cut and weakly (r = 0.279) but significantly (P = 0.037) correlated with the percent cut depth. The roughness grading ranged from 2.63 to 2.56 and showed no trend with the percent cut depth (r = 0.006, P = 0.968). CONCLUSIONS: Compared with previously published results of fresh corneas, in which ridge grading exceeded 3 for cuts deeper than 31%, cut quality was better for the VisionGraft. Even at depths up to 48% of the total stromal thickness, ridge grading was not worse than shallow cuts. Thus, gamma-irradiated corneas could provide a smoother interface than do fresh eye bank corneas for laser-assisted lamellar anterior keratoplasty.

Zhang, X., Wang, K., Yang, Q., Wang, J., Xuan, C., Liu, X. -., et al. (2015). Acute phase proteins altered in the plasma of patients with congenital ventricular septal defect. *Proteomics - Clinical Applications,*

Zhang, Z., Atwell, L. L., Farris, P. E., Ho, E., & Shannon, J. (2015). Associations between cruciferous vegetable intake and selected biomarkers among women scheduled for breast biopsies. *Public Health Nutrition,* , 1-8.

OBJECTIVE: To examine the relationship between dietary cruciferous vegetable intake and selected tumour biomarkers for histone acetylation (H3K9ac, H3K18ac, HDAC3 and HDAC6), proliferation (Ki-67) and cell-cycle regulation (p21) from breast tissue. DESIGN: The study used baseline data of women recruited to participate in a clinical trial of sulforaphane supplement. Dietary cruciferous vegetable intake was collected through a validated Arizona Cruciferous Vegetable Intake Questionnaire. Breast tissue was obtained from biopsy samples. Spearman correlations were calculated between intake of specific cruciferous vegetables and biomarkers. Tissue biomarkers were log2-transformed to obtain approximate normality. Linear regression analyses were conducted to examine associations between cruciferous vegetable intake and

biomarkers adjusting for age and use of non-steroidal anti-inflammatory drugs. False discovery rate (FDR) was used to account for multiple comparisons. SETTING: Clinical trial baseline. SUBJECTS: Fifty-four women who had abnormal mammogram findings and were scheduled for breast biopsy. RESULTS: Mean intake of total cruciferous vegetables from all food sources was 81.7 (sd 57.3) g/d. Mean urinary total sulforaphane metabolites was 0.08 (sd 0.07) microm/mm creatinine. Total cruciferous vegetable intake was inversely associated with Ki-67 protein expression in breast ductal carcinoma in situ (DCIS) tissue (beta=-0.004; se=0.001; FDR q value=0.03), but not in benign or invasive ductal carcinoma (IDC) tissue. No association was found for other biomarkers measured (HDAC3, HDAC6, H3K9, H3K18 and p21) in all tissues examined (benign, DCIS and IDC). CONCLUSIONS: The present study sought to provide additional evidence for the potential role of sulforaphane in histone acetylation and cell proliferation. Here, we report that total cruciferous vegetable intake is associated with decreased cell proliferation in breast DCIS tissue.

Zheng, H. F., Forgetta, V., Hsu, Y. H., Estrada, K., Rosello-Diez, A., Leo, P. J., et al. (2015). Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. *Nature,* The extent to which low-frequency (minor allele frequency (MAF) between 1-5%) and rare (MAF </= 1%) variants contribute to complex traits and disease in the general population is mainly unknown. Bone mineral density (BMD) is highly heritable, a major predictor of osteoporotic fractures, and has been previously associated with common genetic variants, as well as rare, population-specific, coding variants. Here we identify novel non-coding genetic variants with large effects on BMD (ntotal = 53,236) and fracture (ntotal = 508,253) in individuals of European ancestry from the general population. Associations for BMD were derived from whole-genome sequencing (n = 2,882 from UK10K (ref. 10); a population-based genome sequencing consortium), whole-exome sequencing (n = 3,549), deep imputation of genotyped samples using a combined UK10K/1000 Genomes reference panel (n = 26,534), and de novo replication genotyping (n = 20,271). We identified a low-frequency non-coding variant near a novel locus, EN1, with an effect size fourfold larger than the mean of previously reported common variants for lumbar spine BMD (rs11692564(T), MAF = 1.6%, replication effect size = +0.20 s.d., Pmeta = 2 x 10-14), which was also associated with a decreased risk of fracture (odds ratio = 0.85; P = 2 x

10-11; ncases = 98,742 and ncontrols = 409,511). Using an En1cre/flox mouse model, we observed that conditional loss of En1 results in low bone mass, probably as a consequence of high bone turnover. We also identified a novel low-frequency non-coding variant with large effects on BMD near WNT16 (rs148771817(T), MAF = 1.2%, replication effect size = +0.41 s.d., Pmeta = 1 x 10-11). In general, there was an excess of association signals arising from deleterious coding and conserved non-coding variants. These findings provide evidence that low-frequency non-coding variants have large effects on BMD and fracture, thereby providing rationale for whole-genome sequencing and improved imputation reference panels to study the genetic architecture of complex traits and disease in the general population.

Zhou, H., Zhang, L., Wu, L., Zou, X., Luo, X., Xia, K., et al. (2015). Validity and reliability analysis of the chinese parent version of the autism spectrum rating scale (6-18 years). *Psychiatry Research,* This study aimed to investigate the validity and reliability of the Chinese parent version of the Autism Spectrum Rating Scale (ASRS, 6-18 years) for a general sample of Chinese children. The study involved assessing 1625 community-based subjects aged 6-12 years from four sites (Shanghai, Guangzhou, Changsha, and Harbin city) in China and 211 clinic-based participants aged 6-18 with a confirmed diagnosis of autism spectrum disorders (ASDs). The internal consistency (Cronbach's alpha) ranged from 0.585 to 0.929, and the test-retest reliability (interclass correlations) ranged from 0.542 to 0.749, indicating no significant difference between the two tests at an interval of 2-4 weeks. The construct validity was relatively excellent, and the concurrent validity with the Social Responsiveness Scale (SRS) (Pearson correlations) was 0.732 between the two total scores. Receiver operating characteristics (ROC) analyses showed excellent and comparable discriminant validity of the ASRS with respect to the SRS, with an area under the curve (AUC) of 0.9507 (95% CI: 0.93-0.97) versus 0.9703 (95% CI: 0.96-0.98), respectively. Our data suggested a cutoff >/=60 for the Chinese version of the ASRS, with good accuracy in screening autism symptoms (sensitivity=94.2%, specificity=77%). The Chinese parent version of the ASRS is therefore a reliable and valid tool for screening autistic symptoms in Chinese children in general.

Zhu, W., Casper, A., Libal, N. L., Murphy, S. J., Bodhankar, S., Offner, H., et al. (2015). Preclinical evaluation of recombinant T cell receptor ligand RTL1000 as a therapeutic agent in ischemic stroke. *Translational Stroke Research, 6*(1), 60-68.

Recombinant T cell Receptor Ligand 1000 (RTL1000), a partial human major histocompatibility complex (MHC) molecule coupled to a human myelin peptide, reduces infarct size after experimental stroke in HLA-DRB1*1502 transgenic (DR2-Tg) mice. In this study, we characterized the therapeutic time window of opportunity for RTL1000; we explored the efficacy of a single dose of RTL1000 administration and determined if RTL1000 affords long-term neurobehavioral functional improvement after ischemic stroke. Male DR2-Tg mice underwent 60 min of intraluminal reversible middle cerebral artery occlusion (MCAO). RTL1000 or vehicle was injected 4, 6, or 8 h after MCAO, followed by three daily injections. In the single-dose study, one-time injection of RTL1000 was applied 4 h after MCAO. Cortical, striatal, and hemispheric infarct sizes were measured 24 or 96 h after stroke. Behavioral testing, including neuroscore evaluation, open field, paw preference, and novel object recognition, was performed up to 28 days after stroke. Our data showed that RTL1000 significantly reduced the infarct size 96 h after MCAO when the first injection was given at 4 and 6 h, but not 8 h, after the onset of stroke. A single dose of 400 or 100 mug RTL1000 also significantly reduced the infarct size 24 h after MCAO. Behavioral testing showed that RTL1000 treatment used 4 h after MCAO improved long-term cognitive outcome 28 days after stroke. Taken together, RTL1000 protects against acute injury if applied within a 6-h time window and improves long-term functional recovery after experimental stroke in DR2-Tg mice.