

References

Å ileikyte, J., & Forte, M. (2016). Shutting down the pore: The search for small molecule inhibitors of the mitochondrial permeability transition. *Biochimica Et Biophysica Acta - Bioenergetics*,
The mitochondrial permeability transition pore (PTP) is now recognized as playing a key role in a wide variety of human diseases whose common pathology may be based in mitochondrial dysfunction. Recently, PTP assays have been adapted to high-throughput screening approaches to identify small molecules specifically inhibiting the PTP. Following extensive secondary chemistry, the most potent inhibitors of the PTP described to date have been developed. This review will provide an overview of each of these screening efforts, use of resulting compounds in animal models of PTP-based diseases, and problems that will require further study. Å© 2016 Elsevier B.V.

Abraham, I., Alhossan, A., Lee, C. S., Kutbi, H., & Macdonald, K. (2016). 'Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: Systematic review. *Allergy: European Journal of Allergy and Clinical Immunology*,
We reviewed 24 'real-life' effectiveness studies of omalizumab in the treatment of severe allergic asthma that included 4117 unique patients from 32 countries with significant heterogeneity in patients, clinicians and settings. The evidence underscores the short- and long-term benefit of anti-IgE therapy in terms of the following: improving lung function; achieving asthma control and reducing symptomatology, severe exacerbations and associated work/school days lost; reducing healthcare resource utilizations, in particular hospitalizations, hospital lengths of stay and accident specialist or emergency department visits; reducing or discontinuing other asthma medications; and improving quality of life - thus confirming, complementing and extending evidence from randomized trials. Thus, omalizumab therapy is associated with signal improvements across the full objective and subjective burden of illness chain of severe allergic asthma. Benefits of omalizumab may extend up to 2-4 years, and the majority of omalizumab-treated patients may benefit for many years. Omalizumab has positive short- and long-term safety profiles similar to what is known from randomized clinical trials. Initiated patients should be monitored for treatment response at 16 weeks. Those showing positive response at that time

are highly likely to show sustained treatment response and benefit in terms of clinical, quality of life and health resource utilization outcomes. © 2016 John Wiley & Sons A/S.

Ahn, J., Jones, D., Yarris, L. M., & Fromme, H. B. (2016). A national needs assessment of emergency medicine resident-as-teacher curricula. *Internal and Emergency Medicine*,
Both the Liaison Committee on Medical Education and the Accreditation Council of Graduate Medical Education require residents to be engaged in teaching to develop skills as educators. Although proposed guidelines for an emergency medicine (EM) resident-as-teachers (RAT) curriculum were published in 2006, little has been published regarding RAT curriculum implementation or outcomes since. A crucial first step in developing a formal RAT curriculum for EM educators to pilot, implement, and evaluate is an assessment of current needs and practices related to RAT curricula in EM residencies. The aim of this study was to conduct a needs assessment of EM residency programs regarding RAT curricular resources and practices. We invited all EM residency programs to participate in a web-based survey assessing their current RAT curricula and needs. 28 % responded to our needs assessment. Amongst responding programs, 60 % had a RAT curriculum. Of programs with a required medical student rotation, 59 % had a RAT curriculum. Of programs without a RAT program, 14 % had a program in development, and 18 % had a teaching resident program without a curriculum. Most RAT programs (72 %) were lecture-based and the majority (66 %) evaluated using survey data. 84 % of respondent programs demonstrated a desire for a national RAT curriculum. We find that despite national mandates, a large portion of programs do not have a RAT curriculum in place. There is wide variation in core content and curriculum evaluation techniques among available curricula. A majority of respondents report interest in a standardized web-based curriculum as one potential solution to this problem. Our results may help inform collaborative efforts to develop a national EM RAT curriculum.

Ahn, J., Nguyen, M. H., Lim, J. K., Lee, H. M., Pan, C. Q., & Lok, A. S. (2016). Letter: Lessons from the 'real-world' entecavir therapy in chronic hepatitis B patients - authors' reply. *Alimentary Pharmacology & Therapeutics*, 43(7), 847-848.

Akinseye, O. A., Ojike, N. I., Akinseye, L. I., Dhandapany, P. S., & Pandi-Perumal, S. (2016).

Association of sleep duration with stroke in diabetic patients: Analysis of the national health interview survey. *Journal of Stroke and Cerebrovascular Diseases*, 25(3), 650-655.

Background Habitual sleep duration is increasingly being recognized as an important risk factor for stroke. We sought to describe the association between sleep duration and stroke in a cohort of individuals with diabetes. Methods Data from the National Health Interview Survey for the years 2004-2013 were used. Only those answering "yes" to the question "Have you EVER been told by a doctor or other health professional that you have diabetes or sugar diabetes?" were included in the analysis. Sleep duration was categorized as short (≤ 6 hours), normal (7-8 hours), or long (≥ 9 hours). Self-reported diagnosis of stroke was the main outcome of interest. Findings A total number of 26,364 self-reported diabetic individuals provided data for analysis. Stroke was reported in 9.1% of short sleepers, 16.1% of long sleepers, and 8.3% of normative sleepers ($P < .05$). In the unadjusted model, short and long sleepers had an increased odds of stroke compared to normal sleepers (odds ratio OR] = 1.12, 95% confidence interval CI]: 1.02-1.23, $P = .01$; and OR = 2.18, 95% CI: 1.96-2.42, $P = .01$; respectively), but the association between short sleep and stroke became nonsignificant after multivariate adjustment (OR = 1.15, 95% CI: .95-1.40, $P = .16$) except in white participants. The association between long sleep duration and stroke persisted (OR = 1.46, 95% CI: 1.16-1.84, $P = .01$), especially in males (OR = 1.62, 95% CI: 1.14-2.28) and in white participants (OR = 1.97, 95% CI: 1.47-2.65). Conclusion In diabetic patients, abnormal sleep duration was associated with increased risk of stroke, and this association varied among different sex and ethnic groups. © 2016 National Stroke Association. All rights reserved.

Alarcón, G., Ray, S., & Nagel, B. J. (2016). Lower working memory performance in overweight and obese adolescents is mediated by white matter microstructure. *Journal of the International Neuropsychological Society*, 22(3), 281-292.

Objectives: Elevated body mass index (BMI) is associated with deficits in working memory, reduced gray matter volume in frontal and parietal lobes, as well as changes in white matter (WM) microstructure. The current study examined whether BMI was related to working memory performance and blood oxygen level dependent (BOLD) activity, as well as WM microstructure

during adolescence. Methods: Linear regressions with BMI and (1) verbal working memory BOLD signal, (2) spatial working memory BOLD signal, and (3) fractional anisotropy (FA), a measure of WM microstructure, were conducted in a sample of 152 healthy adolescents ranging in BMI. Results: BMI was inversely related to IQ and verbal and spatial working memory accuracy; however, there was no significant relationship between BMI and BOLD response for either verbal or spatial working memory. Furthermore, BMI was negatively correlated with FA in the left superior longitudinal fasciculus (SLF) and left inferior longitudinal fasciculus (ILF). ILF FA and IQ significantly mediated the relationship between BMI and verbal working memory performance, whereas SLF FA, but not IQ, significantly mediated the relationship between BMI and accuracy of both verbal and spatial working memory. Conclusions: These findings indicate that higher BMI is associated with decreased FA in WM fibers connecting brain regions that support working memory, and that WM microstructural deficits may underlie inferior working memory performance in youth with higher BMI. Of interest, BMI did not show the same relationship with working memory BOLD activity, which may indicate that changes in brain structure precede changes in function. © Copyright The International Neuropsychological Society 2015.

Alzhanov, D., & Rotwein, P. (2016). Characterizing a distal muscle enhancer in the mouse *Igf2* locus. *Physiological Genomics*, 48(2), 167-172.

Insulin-like growth factor-2 (IGF2) is highly expressed in skeletal muscle and was identified as a quantitative trait locus for muscle mass. Yet little is known about mechanisms of its regulation in muscle. Recently, a DNA segment found ~100 kb from the *Igf2* gene was identified as a possible muscle transcriptional control element. Here we have developed an in vivo reporter system to assess this putative enhancer by substituting nuclear (n) EGFP for *Igf2* coding exons in a bacterial artificial chromosome containing the mouse *Igf2* - H19 chromosomal locus. After stable transfection into a mesenchymal stem cell line, individual clones were converted to myoblasts and underwent progressive muscle-specific gene expression and myotube formation in differentiation medium. Transgenic mRNA and nuclear-targeted enhanced green fluorescent protein were produced coincident with endogenous *Igf2* mRNA, but only in lines containing an intact distal conserved DNA element. Our results show that a 294 bp DNA fragment containing two E-boxes is a necessary and sufficient long-range enhancer for induction of *Igf2* gene

transcription during skeletal muscle differentiation and provides a robust experimental platform for its further functional dissection. © 2016 the American Physiological Society.

Amini, A., Murphy, B., Cost, C. R., Garrington, T. P., Greffe, B. S., & Liu, A. K. (2016). Cardiac mortality in children and adolescents with hodgkin's lymphoma: A surveillance, epidemiology and end results analysis. *Journal of Adolescent and Young Adult Oncology*,

PURPOSE: The purpose of this study was to evaluate the risk of cardiac death in pediatric Hodgkin's lymphoma (HL) survivors and identify high-risk groups that may need additional surveillance. METHODS: The Surveillance, Epidemiology and End Results program database was queried to analyze the rates of radiation therapy (RT) use and cardiac-specific mortality (CSM) in HL patients, aged 0-21 years, treated from 1973 to 2007. Primary endpoint was cardiac mortality. RESULTS: A total of 6552 patients were included. Median follow-up was 12 years (range, 0-40). Median age at diagnosis was 17 years (range, 0-21). The majority were white (85.5%), from western states (41.2%), had nodular sclerosis HL (73.2%), presented with stage I or II disease (51.5%), and received RT (56.1%). Death from cardiac disease occurred in 114 patients (9.2% of all deaths). CSM for the entire cohort at 10-, 20-, and 30-year time points was 0.3%, 1.6%, and 5.0%, respectively. Median age at the time of cardiac death was 39 years (range, 18-58 years). Under multivariate analysis (MVA), adolescent patients (ages 13-21) had higher rates of CSM (hazard ratio [HR], 3.05; $p = 0.005$). Female gender (HR, 0.43; $p < 0.001$), patients treated from 1998 to 2007 (HR, 0.19; $p = 0.018$), and those with lymphocyte-rich histology (HR, 0.14; $p = 0.047$) had significantly lower rates of CSM. Use of RT was not associated with CSM under MVA (HR, 1.18, $p = 0.452$). CONCLUSION: The cumulative incidence of CSM in this population analysis of pediatric HL was 9.2%, with a steady decline over the past several decades. Adolescent patients at diagnosis and males were more likely to die of cardiac-related causes.

Aminoshariae, A., Kuliid, J. C., & Donaldson, M. (2016). Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects an updated systematic review. *Journal of the American Dental Association*, 147(2), 98-110.

Background In this article, the authors examine the available scientific evidence regarding

adverse effects of short-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Short-term use was defined as 10 days or fewer. Methods The authors reviewed randomized controlled clinical trials and cohort and case-controlled clinical studies published between 2001 and June 2015 in which the investigators reported on the safety of nonselective cyclooxygenase inhibitors and of cyclooxygenase-2 selective inhibitor NSAIDs. Results The systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines allowed the authors to identify 40 studies that met the inclusion criteria. Conclusions On the basis of the available scientific evidence, NSAIDs may be considered relatively safe drugs when prescribed at the most effective dose and for the shortest duration of time, which was defined to be 10 days or fewer. Practical Implications Although the US Food and Drug Administration recommends the use of NSAIDs beyond 10 days to be accompanied by a consultation with a health care provider, the use of NSAIDs may be considered relatively safe when prescribed at the most effective dose and for the shortest duration of time, which was defined as 10 days or fewer. Exceptions would be for patients at risk of developing NSAID-exacerbated respiratory disease, patients with prior myocardial infarction who are receiving antithrombotic therapy, patients with asthma, and patients with a history of renal disease. © 2016 American Dental Association.

Anand, V., Hyun, C., Khan, Q. M., Hall, C., Hessefort, N., Sonnenberg, A., et al. (2016). Identification and fibrosis staging of hepatitis C patients using the electronic medical record system. *Journal of Clinical Gastroenterology*,

BACKGROUND AND AIMS:: The aim of this study was to noninvasively assess the severity of chronic hepatitis C virus (HCV) in large patient populations. It would be helpful if fibrosis scores could be calculated solely on the basis of data contained in the patients'™ electronic medical records (EMR). We performed a pilot study to identify all HCV-infected patients in a large health care system, and predict their fibrosis stage on the basis of demographic and laboratory data using common data from their EMR. MATERIALS AND METHODS:: HCV-infected patients were identified using the EMR. The liver biopsies of 191 HCV patients were graded using the Ishak and Metavir scoring systems. Demographic and laboratory data were extracted from the EMR and used to calculate the aminotransferase to platelet ratio index, Fib-4, Fibrosis Index, Forns, GÅŕteberg University Cirrhosis Index, Lok Index, and Vira-HepC. RESULTS:: In total, 869 HCV-

infected patients were identified from a population of over 1 million. In the subgroup of patients with liver biopsies, all 7 algorithms were significantly correlated with the fibrosis stage. The degree of correlation was moderate, with correlation coefficients ranging from 0.22 to 0.60. For the detection of advanced fibrosis (Metavir 3 or 4), the areas under the receiver operating characteristic curve ranged from 0.71 to 0.84, with no significant differences between the individual scores. Sensitivities, specificities, and positive and negative predictive values were within the previously reported range. All scores tended to perform better for higher fibrosis stages. CONCLUSIONS:: Our study demonstrates that HCV-infected patients can be identified and their fibrosis staged using commonly available EMR-based algorithms. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Andrea, S. B., Siegel, S. A. R., & Teo, A. R. (2016). Social support and health service use in depressed adults: Findings from the national health and nutrition examination survey. *General Hospital Psychiatry, 39*, 73-79.

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

This association is largely attributable to the effect of male gender on the relationship between social support and health service use. © 2015.

Aro, A. L., Phan, D., Teodorescu, C., Uy-Evanado, A., Reinier, K., Gunson, K., et al. (2016). Cardiac structural and functional profile of patients with delayed QRS transition zone and sudden cardiac death. *Europace : European Pacing, Arrhythmias, and Cardiac Electrophysiology : Journal of the Working Groups on Cardiac Pacing, Arrhythmias, and Cardiac Cellular Electrophysiology of the European Society of Cardiology,*

AIMS: Delayed QRS transition zone in the precordial leads of the 12-lead electrocardiogram (ECG) has been recently associated with increased risk of sudden cardiac death (SCD), but the underlying mechanisms are unknown. We correlated echocardiographic findings with ECG and clinical characteristics to investigate how alterations in cardiac structure and function contribute to this risk marker. METHODS AND RESULTS: From the ongoing population-based Oregon Sudden Unexpected Death Study (catchment population approximately 1 million), SCD cases with prior ECG available (n = 627) were compared with controls (n = 801). Subjects with delayed transition at V5 or later were identified, and clinical and echocardiographic patterns associated with delayed transition were analysed. Delayed transition was present in 31% of the SCD cases and 17% of the controls. These subjects were older and more likely to have cardiovascular risk factors and history of myocardial infarction. Delayed transition was associated with increased left ventricular (LV) mass (122.7 +/- 40.2 vs. 102.9 +/- 33.7 g/m²; P < 0.001), larger LV diameter (53.3 +/- 10.4 vs. 49.2 +/- 8.0 mm; P < 0.001), and lower LV ejection fraction (LVEF) (46.4 +/- 15.7 vs. 55.6 +/- 12.5%; P < 0.001). In multivariate analysis, delayed transition was independently associated with myocardial infarction, reduced LVEF, and LV hypertrophy. The association between delayed transition and SCD was independent of the LVEF (OR 1.57; 95% CI 1.04-2.38; P = 0.032). CONCLUSION: The underpinnings of delayed QRS transition zone extend beyond previous myocardial infarction and reduced LVEF. Since the association with sudden death is independent of these factors, this novel marker of myocardial electrical remodelling should be explored as a potential risk predictor of SCD.

Asquith, M., Stauffer, P., Davin, S., Mitchell, C., Lin MDPHD, P., & Rosenbaum, J. T. (2016). Perturbed mucosal immunity and dysbiosis accompany clinical disease in a rat model of spondyloarthritis. *Arthritis & Rheumatology (Hoboken, N.J.)*,

Objective The HLA-B27/beta2 microglobulin (beta2m) transgenic rat is a leading model of B27-associated spondyloarthopathy and disease is dependent on the presence of intestinal bacteria. We have shown previously that adult HLA-B27/beta2m rats have an altered intestinal microbiota. In this study we sought to better define age-dependent changes to both mucosal immune function and dysbiosis in this model. Methods Intestinal contents were collected from wild type and HLA-B27/beta2m+ rats post-weaning (3 and 6 weeks), at disease onset (10 wks) and after the establishment of disease (16 wks). Microbial community structure was determined by 16s sequencing and qRT-PCR. Mucosal and systemic Th1, Th17 and Treg responses were analyzed by flow cytometry, as was the frequency of IgA-coated intestinal bacteria. Intestinal expression of inflammatory cytokines and antimicrobial peptides (AMPs) was determined by qRT-PCR. Results An inflammatory cytokine signature and elevated AMP expression during the post-weaning period preceded the development of clinical bowel inflammation and dysbiosis in HLA-B27/beta2m+ rats. An early and sustained expansion of the Th17 pool was specifically observed in cecal and colonic mucosa of HLA-B27/beta2m rats. Strongly elevated Akkermansia muciniphilia colonization and IgA coating of intestinal bacteria was significantly associated with HLA-B27 expression and arthritis development. Conclusions and Perspectives HLA-B27/beta2m expression in this rat model renders the host hyper-responsive to microbial antigens from infancy. Early activation of innate immunity and expansion of a mucosal Th17 signature are soon followed by dysbiosis in HLA-B27/beta2m+ve animals. Perturbed mucosal immunity and dysbiosis strongly merit further study in both pre-diseased and diseased SpA patient populations. This article is protected by copyright. All rights reserved.

Atkins, D., & Kansagara, D. (2016). Reducing readmissions-destination or journey? *JAMA Internal Medicine*,

Aziz, M. (2015). Advances in laryngoscopy. *F1000research*, 4, 10.12688/f1000research.7045.1. eCollection 2015.

Recent technological advances have made airway management safer. Because difficult intubation remains challenging to predict, having tools readily available that can be used to manage a difficult airway in any setting is critical. Fortunately, video technology has resulted in improvements for intubation performance while using laryngoscopy by various means. These technologies have been applied to rigid optical stylets, flexible intubation scopes, and, most notably, rigid laryngoscopes. These tools have proven effective for the anticipated difficult airway as well as the unanticipated difficult airway.

Aziz, M. F., Abrons, R. O., Cattano, D., Bayman, E. O., Swanson, D. E., Hagberg, C. A., et al. (2016).

First-attempt intubation success of video laryngoscopy in patients with anticipated difficult direct laryngoscopy: A multicenter randomized controlled trial comparing the C-MAC D-blade versus the GlideScope in a mixed provider and diverse patient population. *Anesthesia and Analgesia*, 122(3), 740-750.

BACKGROUND: Intubation success in patients with predicted difficult airways is improved by video laryngoscopy. In particular, acute-Angle video laryngoscopes are now frequently chosen for endotracheal intubation in these patients. However, there is no evidence concerning whether different acute-Angle video laryngoscopes can be used interchangeably in this scenario and would allow endotracheal intubation with the same success rate. We therefore tested whether first-Attempt intubation success is similar when using a newly introduced acute-Angle blade, that is an element of an extended airway management system (C-MAC D-Blade) compared with a well-established acute-Angle video laryngoscope (GlideScope). **METHODS:** In this large multicentered prospective randomized controlled noninferiority trial, patients requiring general anesthesia for elective surgery and presenting with clinical predictors of difficult laryngoscopy were randomly assigned to intubation using either the C-MAC D-Blade or the GlideScope video laryngoscope the hypothesis was that first-Attempt intubation success using the new device (D-Blade) is no >4% less than the established device (GlideScope), which would determine noninferiority of the new instrument versus the established instrument the secondary outcomes we observed included intubation success with multiple attempts and airway-related complications within 7 days of enrollment. **RESULTS:** Eleven hundred patients were randomly assigned to either video laryngoscope. Intubation success rate on first attempt was 96.2% in the GlideScope group and

93.4% in the C-MAC D-Blade group. Although the absolute difference between the 2 groups was only 2.8%, the 90.35% upper confidence limit of the difference exceeded the predefined margin (4.98%), indicating a rejection of the noninferiority hypothesis for first-Attempt intubation success. For attending anesthesiologists, and upon multiple attempts, intubation success did not differ between systems. Pharyngeal injury was noted in 1% of the patients, and the incidence did not differ between interventional groups. CONCLUSIONS: Head-to-head comparison in this large multicenter trial revealed that the newly introduced C-MAC D-Blade does not yield the same first-Attempt intubation success as the GlideScope in patients with predicted difficult laryngoscopy except in the hands of attending anesthesiologists. Additional research would be necessary to identify potential causes for this difference. Intubation success rates were very high with both systems, indicating that acute-Angle video laryngoscopy is an exceptionally successful strategy for the initial approach to endotracheal intubation in patients with predicted difficult laryngoscopy.

Bagchi, R. A., Roche, P., Aroutiounova, N., Espira, L., Abrenica, B., Schweitzer, R., et al. (2016). The transcription factor scleraxis is a critical regulator of cardiac fibroblast phenotype. *BMC Biology*, *14*(1), 21-016-0243-8.

BACKGROUND: Resident fibroblasts synthesize the cardiac extracellular matrix, and can undergo phenotype conversion to myofibroblasts to augment matrix production, impairing function and contributing to organ failure. A significant gap in our understanding of the transcriptional regulation of these processes exists. Given the key role of this phenotype conversion in fibrotic disease, the identification of such novel transcriptional regulators may yield new targets for therapies for fibrosis. RESULTS: Using explanted primary cardiac fibroblasts in gain- and loss-of-function studies, we found that scleraxis critically controls cardiac fibroblast/myofibroblast phenotype by direct transcriptional regulation of myriad genes that effectively define these cells, including extracellular matrix components and alpha-smooth muscle actin. Scleraxis furthermore potentiated the TGFbeta/Smad3 signaling pathway, a key regulator of myofibroblast conversion, by facilitating transcription complex formation. While scleraxis promoted fibroblast to myofibroblast conversion, loss of scleraxis attenuated myofibroblast function and gene expression. These results were confirmed in scleraxis knockout mice, which were cardiac matrix-

deficient and lost ~50 % of their complement of cardiac fibroblasts, with evidence of impaired epithelial-to-mesenchymal transition (EMT). Scleraxis directly transactivated several EMT marker genes, and was sufficient to induce mesenchymal/fibroblast phenotype conversion of A549 epithelial cells. Conversely, loss of scleraxis attenuated TGFbeta-induced EMT marker expression. CONCLUSIONS: Our results demonstrate that scleraxis is a novel and potent regulator of cellular progression along the continuum culminating in the cardiac myofibroblast phenotype. Scleraxis was both sufficient to drive conversion, and required for full conversion to occur. Scleraxis fulfills this role by direct transcriptional regulation of key target genes, and by facilitating TGFbeta/Smad signaling. Given the key role of fibroblast to myofibroblast conversion in fibrotic diseases in the heart and other tissue types, scleraxis may be an important target for therapeutic development.

Bailey, S. R., Marino, M., Hoopes, M., Heintzman, J., Gold, R., Angier, H., et al. (2016). Healthcare utilization after a children's health insurance program expansion in oregon. *Maternal and Child Health Journal*,

Objective The future of the Children's Health Insurance Program (CHIP) is uncertain after 2017. Survey-based research shows positive associations between CHIP expansions and children's healthcare utilization. To build on this prior work, we used electronic health record (EHR) data to assess temporal patterns of healthcare utilization after Oregon's 2009-2010 CHIP expansion. We hypothesized increased post-expansion utilization among children who gained public insurance.

Methods Using EHR data from 154 Oregon community health centers, we conducted a retrospective cohort study of pediatric patients (2-18 years old) who gained public insurance coverage during the Oregon expansion (n = 3054), compared to those who were continuously publicly insured (n = 10,946) or continuously uninsured (n = 10,307) during the 2-year study period. We compared pre-post rates of primary care visits, well-child visits, and dental visits within- and between-groups. We also conducted longitudinal analysis of monthly visit rates, comparing the three insurance groups. Results After Oregon's 2009-2010 CHIP expansions, newly insured patients' utilization rates were more than double their pre-expansion rates [adjusted rate ratios (95 % confidence intervals); increases ranged from 2.10 (1.94-2.26) for primary care visits to 2.77 (2.56-2.99) for dental visits]. Utilization among the newly insured spiked shortly

after coverage began, then leveled off, but remained higher than the uninsured group.

Conclusions This study used EHR data to confirm that CHIP expansions are associated with increased utilization of essential pediatric primary and preventive care. These findings are timely to pending policy decisions that could impact children's access to public health insurance in the United States.

Baldwin, M. K., Edelman, A. B., Lim, J. Y., Nichols, M. D., Bednarek, P. H., & Jensen, J. T. (2016).

Intrauterine device placement at 3 versus 6 weeks postpartum: A randomized trial.

Contraception, 93(4), 356-363.

Objective To investigate whether early placement of an intrauterine device (IUD) at 3 weeks after delivery, compared to placement at 6 weeks, is associated with greater use at 3 months postpartum. **Study Design** This prospective randomized, controlled trial enrolled inpatient postpartum women intending to use intrauterine contraception. Participants were assigned to an early (3 week) or standard (6 week) postpartum visit with IUD placement and were followed for 6 months. We used transvaginal ultrasonography to confirm placement and measure uterine dimensions. We measured pain with IUD insertion and satisfaction with IUD timing using 100-mm visual analog scales. Data were analyzed based on randomization and actual timing of insertion (18-24 vs. 39-45 days). **Results** Between February 2012 and December 2013, 201 subjects were enrolled (early = 101; standard = 100). Most participants returned for IUD placement as scheduled; 70.1% (53/75) in the early group, 74.3% (58/78) in the standard group ($p = .06$). IUD use did not differ between groups at 3 months (73/100, 73.0% and 73/97, 75.3%, respectively, $p = .72$) or 6 months (80.3% and 82.8%, $p = .71$) amongst those women for whom follow-up was available. Women randomized to 6-week insertion were more likely to have resumed intercourse prior to the IUD appointment (15/64, 23.4% vs. 5/68, 7.3%, $p = .01$). Pain with insertion (19.9 vs. 25.1, respectively, $p = .21$) and satisfaction (89.6 vs. 93.4, respectively, $p = .23$) did not vary based on actual timing of insertion. **Conclusion** Offering IUD placement at 3 weeks postpartum compared to standard scheduling at 6 weeks does not result in increased use at 3 months. However, early IUD placement is acceptable to women and without increased pain. **Implications** This study demonstrates that IUD placement as early as 3 weeks postpartum is feasible. Larger studies are needed to evaluate risks and benefits of IUD placement at this early

interval. While earlier timing does not result in increased IUD uptake, early placement should be explored as an option since many women resume intercourse before 6 weeks. © 2016 Elsevier Inc. All rights reserved.

Barnard, D. (2016). Vulnerability and trustworthiness: Polestars of professionalism in healthcare. *Cambridge Quarterly of Healthcare Ethics, 25*(2), 288-300.

Although recent literature on professionalism in healthcare abounds in recommended character traits, attitudes, or behaviors, with a few exceptions, the recommendations are untethered to any serious consideration of the contours and ethical demands of the healing relationship. This article offers an approach based on the professional's commitment to trustworthiness in response to the vulnerability of those seeking professional help. Because our willingness and ability to trust health professionals or healthcare institutions are affected by our personality, culture, race, age, prior experiences with illness and healthcare, and socioeconomic and political circumstances - "the social determinants of trust" - the attitudes and behaviors that actually do gain trust are patient and context specific. Therefore, in addition to the commitment to cultivating attitudes and behaviors that embody trustworthiness, professionalism also includes the commitment to actually gaining a patient's or family's trust by learning, through individualized dialogue, which conditions would win their justified trust, given their particular history and social situation. Copyright © 2016 Cambridge University Press.

Barr, R. D., Ferrari, A., Ries, L., Whelan, J., & Bleyer, W. A. (2016). Cancer in adolescents and young adults: A narrative review of the current status and a view of the future. *JAMA Pediatrics*, Importance: Although cancer remains the most common cause of disease-related death in adolescents and young adults (AYAs) in high-income countries, their overall survival rates continue to increase and now exceed 80% at 5 years in several high-income countries. This has been accomplished through progressive improvements in active treatment and supportive care, although accrual rates to therapeutic clinical trials remain disappointing. Recognition of the unique distribution of diseases in the AYA population with cancer and further understanding of the distinctive biology of cancers in AYAs will lead to continuing gains in clinical outcomes. Observations: Many of the challenges faced by AYAs with a diagnosis of malignant disease are

shared by others with chronic medical conditions and even their healthy peers, such as a sense of invulnerability that may contribute to delays in diagnosis. A particular need for psychological support has been identified for AYAs with cancer, even after active therapy has been completed and especially in the context of palliative care. Notable needs also include fertility preservation and navigation through the multiple transitions in the cancer journey. Additionally, there is a "cost of cure." This is not only in the form of short-term, treatment-related morbidity and mortality but also in the burden of "late effects," including second cancers, that compromise quality of life and limit life expectancy. Establishing clinical programs devoted to AYAs with cancer, with complementary educational initiatives, will strengthen the advances made. It is anticipated that clinical trial accrual will increase substantially, providing further gains in survival. Likewise, addressing the challenges of survivorship, including secondary prevention of long-term morbidity and mortality, will lead to additional improvements in clinical outcomes. Conclusions and Relevance: Transferring this knowledge to the care of an estimated 1 million incident cases of cancer in AYAs worldwide, most of whom do not live in high-income countries, remains a considerable challenge.

Barroso-Gonzalez, J., Auclair, S., Luan, S., Thomas, L., Atkins, K. M., Aslan, J. E., et al. (2016). PACS-2 mediates the ATM and NF-kappaB-dependent induction of anti-apoptotic bcl-xL in response to DNA damage. *Cell Death and Differentiation*,
Nuclear factor kappa B (NF-kappaB) promotes cell survival in response to genotoxic stress by inducing the expression of anti-apoptotic proteins including Bcl-xL, which protects mitochondria from stress-induced mitochondrial outer membrane permeabilization (MOMP). Here we show that the multifunctional sorting protein Pacs-2 (phosphofurin acidic cluster sorting protein-2) is required for Bcl-xL induction following DNA damage in primary mouse thymocytes. Consequently, in response to DNA damage, Pacs-2^{-/-} thymocytes exhibit a blunted induction of Bcl-xL, increased MOMP and accelerated apoptosis. Biochemical studies show that cytoplasmic PACS-2 promotes this DNA damage-induced anti-apoptotic pathway by interacting with ataxia telangiectasia mutated (ATM) to drive NF-kappaB activation and induction of Bcl-xL. However, Pacs-2 was not required for tumor necrosis factor-alpha-induced NF-kappaB activation, suggesting a role for PACS-2 selectively in NF-kappaB activation in response to DNA damage.

These findings identify PACS-2 as an in vivo mediator of the ATM and NF-kappaB-dependent induction of Bcl-xL that promotes cell survival in response to DNA damage. *Cell Death and Differentiation* advance online publication, 4 March 2016; doi:10.1038/cdd.2016.23.

Barry, J. M. (2016). Editorial comment. *Urology*, *88*, 109-110.

Bass, J. K., Knight, K. R., Yock, T. I., Chang, K. W., Cipkala, D., & Grewal, S. S. (2016). Evaluation and management of hearing loss in survivors of childhood and adolescent cancers: A report from the children's oncology group. *Pediatric Blood & Cancer*,

Hearing loss (HL) is common in childhood cancer survivors exposed to platinum chemotherapy and/or cranial radiation and can severely impact quality of life. Early detection and appropriate management can mitigate academic, speech, language, social, and psychological morbidity resulting from hearing deficits. This review is targeted as a resource for providers involved in aftercare of childhood cancers. The goal is to promote early identification of survivors at-risk for HL, appropriate evaluation and interpretation of diagnostic tests, timely referral to an audiologist when indicated, and to increase knowledge of current therapeutic options.

Baston, C., Mancini, M., Rocchi, L., & Horak, F. (2016). Effects of levodopa on postural strategies in parkinson's disease. *Gait and Posture*, *46*, 26-29.

Altered postural control and balance are major disabling issues of Parkinson's disease (PD). Static and dynamic posturography have provided insight into PD's postural deficits; however, little is known about impairments in postural coordination. We hypothesized that subjects with PD would show more ankle strategy during quiet stance than healthy control subjects, who would include some hip strategy, and this stiffer postural strategy would increase with disease progression. We quantified postural strategy and sway dispersion with inertial sensors (one placed on the shank and one on the posterior trunk at L5 level) while subjects were standing still with their eyes open. A total of 70 subjects with PD, including a mild group (H&Yâ‰2, N = 33) and a more severe group (H&Yâ‰3, N = 37), were assessed while OFF and while ON levodopa medication. We also included a healthy control group (N = 21). Results showed an overall preference of ankle strategy in all groups while maintaining balance. Postural strategy was significantly lower ON compared to OFF medication (indicating more hip strategy), but no effect of disease stage was

found. Instead, sway dispersion was significantly larger in ON compared to OFF medication, and significantly larger in the more severe PD group compared to the mild. In addition, increased hip strategy during stance was associated with poorer self-perception of balance. © 2016.

Beadling, C., Wald, A. I., Warrick, A., Neff, T. L., Zhong, S., Nikiforov, Y. E., et al. (2016). A multiplexed amplicon approach for detecting gene fusions by next-generation sequencing. *Journal of Molecular Diagnostics*, 18(2), 165-175.

Chromosomal rearrangements that result in oncogenic gene fusions are clinically important drivers of many cancer types. Rapid and sensitive methods are therefore needed to detect a broad range of gene fusions in clinical specimens that are often of limited quantity and quality. We describe a next-generation sequencing approach that uses a multiplex PCR-based amplicon panel to interrogate fusion transcripts that involve 19 driver genes and 94 partners implicated in solid tumors. The panel also includes control assays that evaluate the $3\text{â}^2/5\text{â}^2$ expression ratios of 12 oncogenic kinases, which might be used to infer gene fusion events when the partner is unknown or not included on the panel. There was good concordance between the solid tumor fusion gene panel and other methods, including fluorescence in situ hybridization, real-time PCR, Sanger sequencing, and other next-generation sequencing panels, because 40 specimens known to harbor gene fusions were correctly identified. No specific fusion reads were observed in 59 fusion-negative specimens. The $3\text{â}^2/5\text{â}^2$ expression ratio was informative for fusions that involved ALK, RET, and NTRK1 but not for BRAF or ROS1 fusions. However, among 37 ALK or RET fusion-negative specimens, four exhibited elevated $3\text{â}^2/5\text{â}^2$ expression ratios, indicating that fusions predicted solely by $3\text{â}^2/5\text{â}^2$ read ratios require confirmatory testing. © 2016 American Society for Investigative Pathology and the Association for Molecular Pathology.

Benedek, G., Zhang, J., Bodhankar, S., Nguyen, H., Kent, G., Jordan, K., et al. (2016). Estrogen induces multiple regulatory B cell subtypes and promotes M2 microglia and neuroprotection during experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology*, 293, 45-53. Sex hormones promote immunoregulatory effects on multiple sclerosis. The current study evaluated estrogen effects on regulatory B cells and resident CNS microglia during experimental autoimmune encephalomyelitis (EAE). Herein, we demonstrate an estrogen-dependent induction

of multiple regulatory B cell markers indicative of IL-10 dependent as well as IFN- γ dependent pathways. Moreover, although estrogen pretreatment of EAE mice inhibited the infiltration of pro-inflammatory cells into the CNS, it enhanced the frequency of regulatory B cells and M2 microglia. Our study suggests that estrogen has a broad effect on the development of regulatory B cells during EAE, which in turn could promote neuroprotection. © 2016 Elsevier B.V.

Berger, K. E., Masterson, J., Mascardo, J., Grapa, J., Appanaitis, I., Temengil, E., et al. (2016). The effects of chewing betel nut with tobacco and pre-pregnancy obesity on adverse birth outcomes among palauan women. *Maternal and Child Health Journal*,
The small Pacific Island nation of Palau has alarmingly high rates of betel nut with tobacco use and obesity among the entire population including pregnant women. This study aimed to determine the effects of betel nut with tobacco use and pre-pregnancy obesity on adverse birth outcomes. This study used retrospective cohort data on 1171 Palauan women who gave birth in Belau National Hospital in Meyuns, Republic of Palau between 2007 and 2013. The exposures of interest were pre-pregnancy obesity and reported betel nut with tobacco use during pregnancy. The primary outcomes measured were preterm birth and low birth weight among full-term infants. A significantly increased risk for low birth weight among full-term infants was demonstrated among those women who chewed betel nut with tobacco during pregnancy when other known risk factors were controlled for. Additionally, pre-pregnancy obesity was associated with a significantly increased risk for preterm birth when other known risk factors were controlled for. Both betel nut with tobacco use and pre-pregnancy obesity were associated with higher risks for adverse birth outcomes. These findings should be used to drive public health efforts in Palau, as well as in other Pacific Island nations where these studies are currently lacking.

Bernacki, G. M., Bahrainy, S., Caldwell, J. H., Levy, W. C., Link, J. M., & Stratton, J. R. (2016). Assessment of the effects of age, gender, and exercise training on the cardiac sympathetic nervous system using positron emission tomography imaging. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*,
BACKGROUND: Using positron emission tomography (PET) imaging, we sought to determine whether normal age or exercise training cause changes in the cardiac sympathetic nervous

system function in male or female healthy volunteers. METHODS: Healthy sedentary participants underwent PET studies before and after 6 months of supervised exercise training. Presynaptic uptake by the norepinephrine transporter-1 function was measured using PET imaging of [11C]-meta-hydroxyephedrine, a norepinephrine analog, and expressed as a permeability-surface area product (PSnt in mL/min/mL). Postsynaptic function was measured as beta-adrenergic receptor density (beta'max in pmol/mL tissue) by imaging the beta-receptor antagonist [11C]-CGP12177. Myocardial blood flow (MBF in mL/min/mL tissue) was measured by imaging [15O]-water. RESULTS: At baseline, there was no age difference in beta'max or MBF but PSnt declined with age (1.12+/-0.11 young vs 0.87+/-0.06 old, p = .036). Before training, women had significantly greater MBF (0.87+/-0.03 vs 0.69+/-0.03, p < .0001) and PSnt (1.14+/-0.08 vs 0.75+/-0.07, p < .001) than men. Training increased VO2 max by 13% (p < .0001), but there were no training effects on beta'max, PSnt, or MBF. Greater MBF in females and a trend to increased PSnt post-training persisted. CONCLUSION: With age, presynaptic uptake as measured by PSnt declines, but there were no differences in beta'max. Endurance training significantly increased VO2 max but did not cause any changes in the measures of cardiac sympathetic nervous system function. These findings suggest that significant changes do not occur or that current PET imaging methods may be inadequate to measure small serial differences in a highly reproducible manner.

Beste, L. A., Mattox, E. A., Pichler, R., Young, B. A., Au, D. H., Kirsh, S. F., et al. (2016). Primary care team members report greater individual benefits from long- versus short-term specialty telemedicine mentorship. *Telemedicine Journal and e-Health : The Official Journal of the American Telemedicine Association*,

BACKGROUND: Primary care providers who participate in structured specialty telemedicine mentorship report improvements in clinical content mastery, professional satisfaction, and specialist communication. INTRODUCTION: Although these programs require investments of infrastructure resources and time, the duration of participation required to accrue optimal benefits is not known. We aimed to assess whether duration of participation is related to improved benefits of a longitudinal telemedicine-based mentorship program, specifically regarding perceived specialty care access, acquisition of new knowledge and skills, team integration, and overall job satisfaction. MATERIALS AND METHODS: We conducted an e-mail

survey of Veterans Affairs-based primary care team members in the United States' Pacific Northwest region who engaged in a longitudinal telemedicine mentorship program (n = 78). RESULTS: After adjustment for potential confounding factors, respondents who engaged in telemedicine mentorship for ≥ 1 year were significantly more likely to strongly agree that telemedicine mentorship improved patient access to specialty care (adjusted odds ratio [AOR] = 9.3, $p < 0.001$) and with perception of integration into a clinical team (AOR = 5.6, $p = 0.01$), but not with overall job satisfaction. CONCLUSION: Telemedicine-based specialty mentorship programs are highly valued by primary care-based participants, and self-reported benefits accumulate beyond 1 year of participation.

Bieber, T., Akdis, C., Lauener, R., Traidl-Hoffmann, C., Schmid-Grendelmeier, P., SchÅppi, G., et al. (2016). Global allergy forum and 3rd davos declaration 2015: Atopic dermatitis/Eczema: Challenges and opportunities toward precision medicine global allergy forum and 3rd davos declaration 2015: Atopic dermatitis/Eczema: Challenges and opportunities toward precision medicine. *Allergy: European Journal of Allergy and Clinical Immunology*,

Bittner, D. O., Ferencik, M., Douglas, P. S., & Hoffmann, U. (2016). Coronary CT angiography as a diagnostic and prognostic tool: Perspective from a multicenter randomized controlled trial: PROMISE. *Current Cardiology Reports*, 18(5), 40-016-0718-9.

The PROMISE (Prospective multicenter imaging study for evaluation of chest pain) trial compared the effectiveness of coronary CT angiography and functional testing as initial diagnostic test for patients with suspicion for stable coronary artery disease (CAD). With 10,003 patients randomized at 193 sites, the PROMISE trial provides a snapshot of real-world care for this very common presentation. Over a median follow-up of 25 months, PROMISE did not find significant differences in major clinical events (composite endpoint 164 vs. 151, HR 1.04 (0.83-1.29); $p = 0.75$) between the two strategies. Other major findings were the large discrepancy between estimates of pre-test likelihood and observed prevalence for obstructive CAD (≥ 50 %) and the proportion of noninvasive tests positive for ischemia or obstructive CAD (53 vs. 11 %; respectively) and the better efficiency of coronary computed tomography angiography (CTA) to

select patients for invasive coronary angiography (ICA) who had obstructive CAD (72 vs. 48 % for coronary CTA and functional testing, respectively). Radiation exposure was higher in the CT arm compared to all functional testing but lower than for nuclear perfusion stress testing. Improvement of patient selection for diagnostic testing and risk stratification will be keys to increase efficacy and efficiency of management of patients with suspicion for stable CAD.

Blackmore, E. R., Gustafsson, H., Gilchrist, M., Wyman, C., & G O'Connor, T. (2016). Pregnancy-related anxiety: Evidence of distinct clinical significance from a prospective longitudinal study. *Journal of Affective Disorders, 197*, 251-258.

BACKGROUND: Pregnancy-related anxiety (PrA) has attracted considerable research attention, but questions remain about its distinctiveness from conventional constructs and measures. In a high psychosocial risk, ethnically diverse sample, we examine the degree to which PrA is distinct from continuous and diagnostic measures of anxiety and worry in terms of longitudinal course, associations with psychosocial and perinatal risk, and prediction of postnatal mood disturbance.

METHODS: 345 women oversampled for prenatal anxiety and depression were selected from an urban obstetrics clinic serving a predominantly low-income, ethnically diverse population. PrA was assessed at 20 and 32 weeks gestation; anxiety and depression symptoms were assessed from questionnaire and from clinical interview at 20 and 32 weeks gestation and again at 2 and 6 months postnatally. Data relevant to psychosocial and obstetric risks were ascertained from interview, medical exam, and chart review. **RESULTS:** Two distinct factors of PrA were identified, indexing specific concerns about the child's health and about the birth; these two PrA factors showed distinct longitudinal patterns in the prenatal period, and modest associations with general measures of anxiety and depression from questionnaire and clinical interview. PrA was also distinguished from conventional symptom measures in its associated features and prediction of birth weight and postnatal mood. **LIMITATIONS:** The sample was at high psychosocial risk and ethnically diverse; findings may not generalize to other samples. **CONCLUSIONS:** PrA can be distinguished from general measures of anxiety in pregnancy in terms of longitudinal course, associated features, and prediction to postnatal mood disturbance, and may warrant specific clinical attention.

Bleyer, A., Baines, C., & Miller, A. B. (2016). Impact of screening mammography on breast cancer mortality. *International Journal of Cancer*, 138(8), 2003-2012.

The degree to which observed reductions in breast cancer mortality is attributable to screening mammography has become increasingly controversial. We examined this issue with three fundamentally different approaches: (i) Chronology - the temporal relationship of the onset of breast cancer mortality decline and the national implementation of screening mammography; (ii) Magnitude - the degree to which breast cancer mortality declined relative to the amount (penetration) of screening mammography; (iii) Analogy - the pattern of mortality rate reductions of other cancers for which population screening is not conducted. Chronology and magnitude were assessed with data from Europe and North America, with three methods applied to magnitude. A comparison of eight countries in Europe and North America does not demonstrate a correlation between the penetration of national screening and either the chronology or magnitude of national breast cancer mortality reduction. In the United States, the magnitude of the mortality decline is greater in the unscreened, younger women than in the screened population and regional variation in the rate of breast cancer mortality reduction is not correlated with screening penetrance, either as self-reported or by the magnitude of screening-induced increase in early-stage disease. Analogy analysis of United States data identifies 14 other cancers with a similar distinct onset of mortality reduction for which screening is not performed. These five lines of evidence from three different approaches and additional observations discussed do not support the hypothesis that mammography screening is a primary reason for the breast cancer mortality reduction in Europe and North America. © 2015 UICC.

Bleyer, L., Huidekoper, H. H., Vaz, F. M., Singh, R., Steiner, R. D., & Debarber, A. E. (2016). Update on newborn dried bloodspot testing for cerebrotendinous xanthomatosis: An available high-throughput liquid-chromatography tandem mass spectrometry method. *Molecular Genetics and Metabolism Reports*, 7, 11-15.

Background Cerebrotendinous xanthomatosis (CTX) is a rare genetic disorder of bile acid synthesis that can cause progressive neurological damage and premature death. Detection of CTX in the newborn period would be beneficial since an effective treatment is available. We previously described a liquid chromatography-electrospray ionization-tandem mass spectrometry

(LC-ESI-MS/MS) test with potential to screen newborn dried bloodspots (DBS) for CTX. We report here modifications to the methodology and application of the modified test to analysis of DBS from a CTX-affected and unaffected newborns. Methods The testing methodology utilizes keto derivatization to enable sensitive LC-ESI-MS/MS measurement of elevated $7\hat{I}\pm,12\hat{I}\pm$ -dihydroxy-4-cholesten-3-one ($7\hat{I}\pm12\hat{I}\pm C4$) in CTX newborn DBS. We report here method modifications, including use of a DBS extraction procedure used in newborn screening laboratories and a reduced analysis time of 2 min per sample. Results Rapid isotope-dilution LC-ESI/MS/MS quantification of the ketosterol bile acid precursor $7\hat{I}\pm12\hat{I}\pm C4$ provides a test that could readily discriminate a CTX positive newborn DBS sample (with a concentration of 104.4 ng/ml) from unaffected newborn samples (with a mean concentration of $4.1 \hat{A}\pm 3.4$ ng/ml; range 0.2-15.6 ng/ml, n = 39) analyzed in a blinded manner. Conclusions We provide additional evidence suggesting $7\hat{I}\pm12\hat{I}\pm C4$ may be a promising test marker to screen newborn DBS for CTX. Early detection and intervention through newborn screening would greatly benefit those affected with CTX, preventing morbidity and mortality. Â© 2016 The Authors. Published by Elsevier Inc.

Bohnen, J. D., Ramly, E. P., Sangji, N. F., de Moya, M., Yeh, D. D., Lee, J., et al. (2016). Perioperative risk factors impact outcomes in emergency versus non-emergency surgery differently - time to separate our national risk-adjustment models? *The Journal of Trauma and Acute Care Surgery*, BACKGROUND: Emergency surgery (ES) is acknowledged to be riskier than Non-Emergency Surgery (NES). Yet, little is known about the relative impact of individual perioperative risk factors on 30-day outcomes in ES vs. NES. METHODS: Using the 2011-2012 ACS-NSQIP nationwide database, the 20 most common ES procedures were identified by CPT code. CPT codes with <300 observations in either ES or NES were excluded. ES cases were defined as "Emergent" & "non-elective" per ACS-NSQIP criteria. Multivariable regression models were constructed to identify predictors of 30-day major morbidity or mortality (MMM) in each group, controlling for demographics, ASA class, comorbidities, preoperative laboratory values, and procedure type. The odds ratios of independent predictors of MMM in ES and NES were derived then individually compared between the two groups; "effect modification" of procedure status (ES vs. NES) on each risk factor was subsequently calculated. RESULTS: Of 986,034 patients, 170,131 met inclusion criteria (59,949 ES, 110,182 NES). The overall risk of MMM was

significantly higher in ES vs. NES (16.75% vs. 9.73%, $p < 0.001$; OR 1.18 (95% CI 1.12-1.24, $p < 0.001$)). Of 40 ES and 38 NES-identified independent risk factors, preoperative transfusion and white blood cell count (WBC) ≤ 4.5 carried significantly higher relative risk of MMM in ES vs. NES. Conversely, ascites, preoperative anemia, and WBC 11-25 carried greater relative risk for MMM in NES. Four procedures (laparoscopic cholecystectomy, laparotomy, umbilical and incisional herniorrhaphy) were inherently riskier in ES vs. NES. The effect modification of ES (vs. NES) ranged between 0.68 [0.52-0.88] for ascites, and 2.56 [1.67-3.92] for umbilical hernia repair. CONCLUSIONS: Perioperative risk factors and procedure type impact postoperative morbidity and mortality differently in ES vs. NES. Instead of using the same risk-adjustment model for both ES and NES, as currently practiced, our findings strongly suggest the need to benchmark emergent and elective surgeries separately.

Boise, L., Hinton, L., Rosen, H. J., & Ruhl, M. (2016). Will my soul go to heaven if they take my brain?

beliefs and worries about brain donation among four ethnic groups. *The Gerontologist*,

PURPOSE OF THE STUDY: Studying the brain through autopsy is an essential component of Alzheimer's disease research. Racial and ethnic minorities are underrepresented in Alzheimer's research generally and, in particular, in the number of completed brain autopsies. We explored beliefs about and attitudes toward brain donation among African American, Chinese, Caucasian, and Latino research subjects and their family members through focus groups at 4 NIH-funded Alzheimer's Disease Centers. DESIGN AND METHODS: Eighteen focus groups were conducted with 61 research subjects and 34 family members. Because the primary purpose of the focus groups was to identify the range of considerations that may influence the decision to participate in brain donation, data from focus groups were pooled and then analyzed. RESULTS: We found that many of the concerns, attitudes, and beliefs about brain donation were similar across the 4 ethnic groups. Concerns and attitudes fell into 3 categories: (a) concerns and misconceptions about brain research and the process of brain removal, (b) religious beliefs, and (c) the role of the family. IMPLICATIONS: Our findings suggest that interventions to enhance enrollment in brain donation that target factors identified in this study are likely to be relevant to people from a broad range of backgrounds and ethnicities. Nonetheless, we observed some potential differences among racial/ethnic groups that may affect how research volunteers and their families approach

a decision about donating their brain for research. Further study is warranted to explore these and other possible culturally distinct attitudes and beliefs about brain donation.

Bokma, J. P., Burchill, L. J., Kovacs, A. H., Oechslin, E. N., Khairy, P., Mulder, B. J. M., et al. (2016). Fellows' perspectives on training in adult congenital heart disease: Results of a survey from the international society for adult congenital heart disease (ISACHD). *International Journal of Cardiology*, 202, 253-255.

Bonde, A. A., Korngold, E. K., Foster, B. R., Westphalen, A. C., Pettersson, D. R., Troxell, M. L., et al. (2016). Prostate cancer with a pseudocapsule at MR imaging: A marker of high grade and stage disease? *Clinical Imaging*, 40(3), 365-369.

Clinicopathological correlates of prostate cancer associated with a pseudocapsule at T2-weighted magnetic resonance (MR) imaging are presented in a retrospective series of 15 patients. Of 15 tumors, 14 involved the peripheral zone. Extracapsular extension was seen in 14 cases. Tumor Gleason score was 8 or above in 12 of 15 cases, and ductal type adenocarcinoma was identified in 4 cases. Step section histopathological correlation (n = 5) demonstrated that the pseudocapsule corresponded with dense compressive or reactive peritumoral fibrosis. A pseudocapsule around prostate cancer at T2-weighted MR imaging is a rare finding that appears to be associated with high grade and stage disease. © 2016 Elsevier Inc..

Borate, U., Mehta, A., Reddy, V., Tsai, M., Josephson, N., & Schnadig, I. (2016). Treatment of CD30-positive systemic mastocytosis with brentuximab vedotin. *Leukemia Research*, 44, 25-31.

Systemic mastocytosis is a myeloproliferative neoplasm with varying presentation that is caused by infiltration of neoplastic mast cells into extracutaneous tissues. Cytoreductive therapy is used to control organ dysfunction in aggressive systemic mastocytosis and is sometimes needed for control of severe refractory symptoms in patients with indolent disease. However, current standard cytoreductive agents are limited by their suboptimal degree and duration of response and associated significant toxicities, highlighting the need for novel treatments for systemic mastocytosis. Recent studies have identified CD30 as a therapeutic target in systemic mastocytosis, as CD30 is expressed on a majority of neoplastic mast cells. In this case series, the clinical outcomes of 4 patients with aggressive or indolent systemic mastocytosis treated with the

anti-CD30 antibody-drug conjugate brentuximab vedotin are reported. Two patients showed evidence of a response to treatment with a reduction in disease burden, 1 of which has demonstrated a durable response with ongoing benefit for more than 3 years. Treatment with brentuximab vedotin was well-tolerated with side effects that were effectively managed by dose modifications. The results presented suggest that brentuximab vedotin is active in systemic mastocytosis and can induce durable responses with a manageable toxicity profile.

Borggreve, J., de Buhr, T., Shrestha, S., Marshall, L. M., Orwoll, E., Peters, K., et al. (2016).

Association of 3-D geometric measures derived from quantitative computed tomography with hip fracture risk in older men. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*,

We investigated the associations of 3-D geometric measures and volumetric BMD (vBMD) of the proximal femur assessed by quantitative computed tomography (QCT) with hip fracture risk among elderly men. Prospective case-cohort design nested within the Osteoporotic Fractures in Men Study (MrOS) cohort. QCT scans of 230 men (65 with confirmed hip fractures) were evaluated with Mindways' QCTPRO-BIT software. Measures that are indicative of bone strength for the femoral neck (FN) and for the trochanteric region (TR) were defined. Bending strength measures were estimated by minimum section modulus, buckling strength by buckling ratio and a local thinning index (LTI). Integral and trabecular vBMD measures were also derived. Areal BMD (aBMD) of the total proximal femur from DXA is presented for comparison. Associations of skeletal measures with incident hip fracture were estimated with hazard ratios (HR) per standard deviation and their 95% confidence intervals (CI) from Cox proportional hazard regression models with adjustment for age, BMI, site and aBMD. Men with hip fractures were older than men without fracture (77.1 +/- 6.0 years vs. 73.3 +/- 5.7 years, $p < 0.01$). Age, BMI and site adjusted HRs were significant for all measures except TR_LTI. Total femoral BMD by DXA (HR = 4.9, 95%CI: 2.5,9.9), and QCT (HR = 5.5, 95%CI: 2.5,11.7), showed the strongest association followed by QCT FN integral vBMD (HR = 3.6, 95%CI:1.8,6.9). In models that additionally included aBMD, FN buckling ratio (HR = 1.9, 95%CI:1.1,3.2) and trabecular vBMD of the TR (HR = 2.0, 95%CI:1.2,3.4) remained associated with hip fracture risk, independent of aBMD. QCT derived 3-D geometric indices of instability of the proximal femur were significantly associated

with incident hip fractures, independent of DXA aBMD. Buckling of the FN is a relevant failure mode not entirely captured by DXA. Further research to study these relationships in women is warranted. This article is protected by copyright. All rights reserved.

Breen, M., Villeneuve, D. L., Ankley, G. T., Bencic, D., Breen, M. S., Watanabe, K. H., et al. (2016).

Computational model of the fathead minnow hypothalamic-pituitary-gonadal axis: Incorporating protein synthesis in improving predictability of responses to endocrine active chemicals.

Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology, 183-184, 36-45.

There is international concern about chemicals that alter endocrine system function in humans and/or wildlife and subsequently cause adverse effects. We previously developed a mechanistic computational model of the hypothalamic-pituitary-gonadal (HPG) axis in female fathead minnows exposed to a model aromatase inhibitor, fadrozole (FAD), to predict dose-response and time-course behaviors for apical reproductive endpoints. Initial efforts to develop a computational model describing adaptive responses to endocrine stress providing good fits to empirical plasma 17β -estradiol (E2) data in exposed fish were only partially successful, which suggests that additional regulatory biology processes need to be considered. In this study, we addressed shortcomings of the previous model by incorporating additional details concerning CYP19A (aromatase) protein synthesis. Predictions based on the revised model were evaluated using plasma E2 concentrations and ovarian cytochrome P450 (CYP) 19 A aromatase mRNA data from two fathead minnow time-course experiments with FAD, as well as from a third 4-day study. The extended model provides better fits to measured E2 time-course concentrations, and the model accurately predicts CYP19A mRNA fold changes and plasma E2 dose-response from the 4-d concentration-response study. This study suggests that aromatase protein synthesis is an important process in the biological system to model the effects of FAD exposure. © 2016 Published by Elsevier Inc.

Broberg, C. S. (2016). Challenges and management issues in adults with cyanotic congenital heart disease. *Heart*,

Brott, T. G., Howard, G., Roubin, G. S., Meschia, J. F., Mackey, A., Brooks, W., et al. (2016). Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *The New England Journal of Medicine*, 374(11), 1021-1031.

BACKGROUND: In the Carotid Revascularization Endarterectomy versus Stenting Trial, we found no significant difference between the stenting group and the endarterectomy group with respect to the primary composite end point of stroke, myocardial infarction, or death during the periprocedural period or any subsequent ipsilateral stroke during 4 years of follow-up. We now extend the results to 10 years. METHODS: Among patients with carotid-artery stenosis who had been randomly assigned to stenting or endarterectomy, we evaluated outcomes every 6 months for up to 10 years at 117 centers. In addition to assessing the primary composite end point, we assessed the primary end point for the long-term extension study, which was ipsilateral stroke after the periprocedural period. RESULTS: Among 2502 patients, there was no significant difference in the rate of the primary composite end point between the stenting group (11.8%; 95% confidence interval [CI], 9.1 to 14.8) and the endarterectomy group (9.9%; 95% CI, 7.9 to 12.2) over 10 years of follow-up (hazard ratio, 1.10; 95% CI, 0.83 to 1.44). With respect to the primary long-term end point, postprocedural ipsilateral stroke over the 10-year follow-up occurred in 6.9% (95% CI, 4.4 to 9.7) of the patients in the stenting group and in 5.6% (95% CI, 3.7 to 7.6) of those in the endarterectomy group; the rates did not differ significantly between the groups (hazard ratio, 0.99; 95% CI, 0.64 to 1.52). No significant between-group differences with respect to either end point were detected when symptomatic patients and asymptomatic patients were analyzed separately. CONCLUSIONS: Over 10 years of follow-up, we did not find a significant difference between patients who underwent stenting and those who underwent endarterectomy with respect to the risk of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke. The rate of postprocedural ipsilateral stroke also did not differ between groups. (Funded by the National Institutes of Health and Abbott Vascular Solutions; CREST ClinicalTrials.gov number, NCT00004732.).

Burrai, F., Hasan, W., Fancourt, D., Luppi, M., & Di Somma, S. (2016). A randomized controlled trial of listening to recorded music for heart failure patients: Study protocol. *Holistic Nursing Practice*, 30(2), 102-115.

Aims. To describe a conceptual framework and to test the effectiveness of a recorded music-listening protocol on symptom burden and quality of life in heart failure (HF) patients.

Background. Heart failure is an important public health problem. Many HF patients experience symptoms burden and poor quality of life, even with current improvements in pharmacological treatments. Recorded music listening has been shown to improve outcomes in cardiovascular patients, but it has never been tested on HF patients and with a specific music protocol and a randomized controlled trial methodology. Methods. This study is a multicenter blinded randomized controlled trial that will involve 150 patients. Eligible patients will have a diagnosis of HF, in New York Heart Association functional classification of I to III, and will be recruited from 3 large hospitals in Northern Italy. Patients will be randomly allocated in a 1:1 ratio to receive recorded music-listening intervention with or without standard care for 3 months. Data will be collected at baseline and at the end of the first, second, and third month during the intervention, and at 6 months for follow-up. The following variables will be collected from HF patients with validated protocols: quality of life (primary endpoint), use of emergency services, rehospitalization rates, all cause mortality, self-care, somatic symptoms, quality of sleep, anxiety and depression symptoms, and cognitive function. Discussion. This study will examine the effect of recorded music listening on HF patients and will inform clinical practice. If the findings are found to be positive, the protocol could be used as a tool for evidence-based applications of recorded music in HF patients. The framework developed in this study may be helpful for future research focused on the effects of music in HF patients. Copyright © 2016 Wolters Kluwer Health, Inc.

Buss, B. A., Schulz, L. T., Reed, K. D., & Fox, B. C. (2016). MALDI-TOF utility in a region with low antibacterial resistance rates. *Clinical Infectious Diseases*, 62(5), 666-667.

Calderwood, A. H., Enestvedt, B. K., Devivo, R., & Schmitt, C. M. (2016). Impact of gender on requests for ASGE leadership assignments. *Gastrointestinal Endoscopy*, 83(4), 730-733.

Background and Aims Committee membership in gastroenterology national societies is considered prestigious, opening the door for leadership roles and professional advancement. Some have hypothesized that women ask for leadership opportunities less frequently than men. Our aim was

to examine the gender representation of requests for placement on an American Society for Gastrointestinal Endoscopy (ASGE) committee. **Methods** We analyzed deidentified records of all requests for assignment to ASGE committees from 2011 to 2014, including applicant's gender, prior service to ASGE, year of application, and whether the applicant was appointed. The primary outcome was the proportion of requests from women compared with the overall ASGE female membership. **Results** There were 513 requests for ASGE committee appointments; 101 (20%) were from women, exceeding the active ASGE female membership (15%; $P = .004$). Overall, the total number of committee requests increased over time from 89 to 195 ($P = .08$); the proportion of requests from women remained stable at 16% to 21% ($P = .51$). Compared with men, women were significantly less likely to have had previous ASGE service (28% vs 42%; $P = .01$) and more likely to have a statement of endorsement from a mentor (33% vs 24%; $P = .06$). The rate of appointment to a committee was 47% (95% confidence interval [CI], 41-52) overall, 42% (95% CI, 37-48) for male applicants, and 65% (95% CI, 54-76) for female applicants. Female gender (odds ratio [OR] 2.6; 1.5-4.5), endorsement from a mentor (OR 3.4; 2.1-5.6), and prior ASGE service (OR 2.3; 1.5-3.5) predicted committee appointment. **Conclusions** For ASGE committee appointments, it appears that women who make requests are successful in receiving these appointments. Future work should evaluate requests and appointments by gender among other gastroenterology societies and explore whether service translates into leadership opportunities for women. © 2016 American Society for Gastrointestinal Endoscopy.

Canales, B. K., Sinclair, L., Kang, D., Mench, A. M., Arreola, M., & Bird, V. G. (2016). Changing default fluoroscopy equipment settings decreases entrance skin dose in patients. *Journal of Urology*, Purpose: Proper fluoroscopic education and protocols may reduce the patient radiation dose but few prospective studies in urology have been performed. Using optically stimulated luminescent dosimeters we tested whether fluoroscopy time and/or entrance skin dose would decrease after educational and radiation reduction protocols. **Materials and Methods:** At default manufacturer settings fluoroscopy time and entrance skin dose were prospectively measured using optically stimulated luminescent dosimeters in patients undergoing ureteroscopy, retrograde pyelogram/stent or percutaneous nephrolithotomy with access for stone disease. A validated radiation safety competency test was administered to urology faculty and residents before and

after web based, hands-on fluoroscopy training. Default fluoroscopy settings were changed from continuous to intermittent pulse rate and from standard to half-dose output. Fluoroscopy time and entrance skin dose were then measured again. Results: The cohorts of 44 pre-protocol and 50 post-protocol patients with stones were similarly matched. The change in mean fluoroscopy time and entrance skin dose from pre-protocol to post-protocol was -0.6 minutes and -11.6 mGy (33%) for percutaneous nephrolithotomy ($p = 0.62$ and <0.001), 0.5 minutes and -0.1 mGy (34%) for ureteroscopy ($p = 0.42$ and 0.31), and 0.1 minute and -0.1 mGy (29%) for retrograde pyelogram/stent ($p = 0.85$ and 0.49 , respectively). Urologist post-training test scores increased 30% from pretraining scores ($p = 0.1$). Conclusions: Radiation safety training protocols improved clinical knowledge but did not significantly alter fluoroscopy time. Changing equipment default settings to intermittent pulse rate (12 frames per second) and half-dose lowered the entrance skin dose by 30% across all endourology patients but most significantly during percutaneous nephrolithotomy. To limit patient radiation exposure fluoroscopy default settings should be decreased before all endourology procedures and image equipment manufacturers should consider lowering standard default renal settings. © 2016 American Urological Association Education and Research, Inc.

Carpenter, R. S., Iwuchukwu, I., Hinkson, C. L., Reitz, S., Lee, W., Kukino, A., et al. (2016). High-dose estrogen treatment at reperfusion reduces lesion volume and accelerates recovery of sensorimotor function after experimental ischemic stroke. *Brain Research*, Estrogens have previously been shown to protect the brain against acute ischemic insults, by potentially augmenting cerebrovascular function after ischemic stroke. The current study hypothesized that treatment with sustained release of high-dose 17beta-estradiol (E2) at the time of reperfusion from middle cerebral artery occlusion (MCAO) in rats would attenuate reperfusion injury, augment post-stroke angiogenesis and cerebral blood flow, and attenuate lesion volume. Female Wistar rats underwent ovariectomy, followed two weeks later by transient, two-hour right MCAO (tMCAO) and treatment with E2 ($n=13$) or placebo (P; $n=12$) pellets starting at reperfusion. E2 treatment resulted in significantly smaller total lesion volume, smaller lesions within striatal and cortical brain regions, and less atrophy of the ipsilateral hemisphere after six weeks of recovery. E2-treated animals exhibited accelerated recovery of contralateral

forelimb sensorimotor function in the cylinder test. Magnetic resonance imaging (MRI) showed that E2 treatment reduced the formation of lesion cysts, decreased lesion volume, and increased lesional cerebral blood flow (CBF). Ktrans, a measure of vascular permeability, was increased in the lesions. This finding, which represents lesion neovascularization, was not altered by E2 treatment. Ischemic stroke-related angiogenesis and vessel formation was confirmed with immunolabeling of brain tissue and was not altered with E2 treatment. In summary, E2 treatment administered immediately following reperfusion significantly reduced lesion size, cyst formation, and brain atrophy while improving lesional CBF and accelerating recovery of functional deficits in a rat model of ischemic stroke.

Carraccio, C., Englander, R., Gilhooly, J., Mink, R., Hofkosh, D., Barone, M. A., et al. (2016). Building a framework of entrustable professional activities, supported by competencies and milestones, to bridge the educational continuum. *Academic Medicine : Journal of the Association of American Medical Colleges*,

The transition to competency-based medical education (CBME) and adoption of the foundational domains of competence by the Accreditation Council for Graduate Medical Education, Association of American Medical Colleges (AAMC), and American Board of Medical Specialties' certification and maintenance of certification (MOC) programs provided an unprecedented opportunity for the pediatrics community to create a model of learning and assessment across the continuum. Two frameworks for assessment in CBME have been promoted: (1) entrustable professional activities (EPAs) and (2) milestones that define a developmental trajectory for individual competencies. EPAs are observable and measurable units of work that can be mapped to competencies and milestones critical to performing them safely and effectively. The pediatrics community integrated the two frameworks to create a potential pathway of learning and assessment across the continuum from undergraduate medical education (UME) to graduate medical education (GME) and from GME to practice. The authors briefly describe the evolution of the Pediatrics Milestone Project and the process for identifying EPAs for the specialty and subspecialties of pediatrics. The method of integrating EPAs with competencies and milestones through a mapping process is discussed, and an example is provided. The authors illustrate the alignment of the AAMC's Core EPAs for Entering Residency with the general pediatrics EPAs and, in turn, the alignment of the

latter with the subspecialty EPAs, thus helping build the bridge between UME and GME. The authors propose how assessment in GME, based on EPAs and milestones, can guide MOC to complete the bridge across the education continuum.

Carter, E. B., Tuuli, M. G., Caughey, A. B., Odibo, A. O., Macones, G. A., & Cahill, A. G. (2016).

Number of prenatal visits and pregnancy outcomes in low-risk women. *Journal of Perinatology*, 36(3), 178-181.

Objective: We investigated the association between number of prenatal visits (PNV) and pregnancy outcomes. Study Design: A retrospective cohort of 12 092 consecutive, uncomplicated term births was included. Exclusion criteria included unknown or third trimester pregnancy dating, pre-existing medical conditions and common pregnancy complications. Patients with ≤ 10 PNV were compared with those with > 10 . The primary outcome was a neonatal composite including neonatal intensive-care unit admission, low APGAR score (≤ 10 PNV and the remaining 70% (N=5093) had ≤ 10 , respectively. There was no difference in the neonatal composite between the two groups. However, women with > 10 PNV were more likely to undergo induction of labor and cesarean delivery. Conclusion: Low-risk women with ≤ 10 PNV had higher rates of pregnancy interventions without improvement in neonatal outcomes. © 2016 Nature America, Inc.

Caspi, R. R., Dick, A., Forrester, J., Klein, R., Niederkorn, J. Y., Paulsen, F., et al. (2016). Immunology of uveitis. (pp. 39-81) Springer Berlin Heidelberg.

Today we are able to differentiate approximately a hundred entities of intraocular inflammations and group them into anatomical types like anterior, intermediate, posterior, and panuveitis. This book will cover most of the reported entities. A few of these entities have highly typical clinical findings, so that the specialist easily may be able to determine the entity, leading to therapy. But a lot of entities develop similarities in their clinical appearance (similar endothelial precipitates, similar chorioretinal infiltrations, similar retinal necrosis) and also similar complications (elevated intraocular pressure, cataract formation, and macular edema). © Springer-Verlag Berlin Heidelberg 2016.

Caughey, A. B., & Snowden, J. M. (2016). Measuring perinatal complications: Different approaches depending on who is at risk. *Paediatric and Perinatal Epidemiology*, *30*(1), 23-24.

Cauley, J. A., Cawthon, P. M., Peters, K. E., Cummings, S. R., Ensrud, K. E., Bauer, D. C., et al.

(2016). Risk factors for hip fracture in older men: The osteoporotic fractures in men study (MrOS). *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*,

Almost 30% of hip fractures occur in men; the mortality, morbidity and loss of independence after hip fractures are greater in men than women. To comprehensively evaluate risk factors for hip fracture in older men, we performed a prospective study of 5,994 men, primarily Caucasian, age 65+ recruited at 6 US clinical centers. During a mean of 8.6 years of 97% complete follow-up, 178 men experienced incident hip fractures. Information on risk factors including femoral neck bone mineral density (FNBMD) was obtained at the baseline visit. Cox proportional hazards models were used to calculate the hazard ratio (HR) with 95% confidence intervals; Fine and Gray models adjusted for competing mortality risk. Older age (≥ 75 years), low FNBMD, currently smoking, greater height and height loss since age 25, history of fracture, use of tricyclic antidepressants, history of myocardial infarction or angina, hyperthyroidism or Parkinson's disease, lower protein intake and lower executive function were all associated with an increased hip fracture risk. Further adjustment for competing mortality attenuated HR for smoking, hyperthyroidism and Parkinson's disease. The incidence rate of hip fracture per 1000 person years (PY) was greatest in men with FNBMD T-scores ≤ -2.5 with 3+ major comorbidities experienced hip fracture at rates of 14.52 vs 0.88 per 1000 PY in men age <70 with zero comorbidities. Older men with low FNBMD, multiple risk factors and multimorbidity have a high risk of hip fracture. Many of these assessments can easily be incorporated into routine clinical practice and may lead to improved risk stratification. This article is protected by copyright. All rights reserved.

Caviness, K., Bughio, F., Crawford, L. B., Streblow, D. N., Nelson, J. A., Caposio, P., et al. (2016).

Complex interplay of the UL136 isoforms balances cytomegalovirus replication and latency. *Mbio*, *7*(2), 10.1128/mBio.01986-15.

Human cytomegalovirus (HCMV), a betaherpesvirus, persists indefinitely in the human host through poorly understood mechanisms. The UL136 gene is carried within a genetic locus important to HCMV latency termed the UL133/8 locus, which also carries UL133, UL135, and UL138. Previously, we demonstrated that UL136 is expressed as five protein isoforms ranging from 33-kDa to 19-kDa, arising from alternative transcription and, likely, translation initiation mechanisms. We previously showed that the UL136 isoforms are largely dispensable for virus infection in fibroblasts, a model for productive virus replication. In our current work, UL136 has emerged as a complex regulator of HCMV infection in multiple contexts of infection relevant to HCMV persistence: in an endothelial cell (EC) model of chronic infection, in a CD34(+) hematopoietic progenitor cell (HPC) model of latency, and in an in vivo NOD-scid IL2Rgammac (null) humanized (huNSG) mouse model for latency. The 33- and 26-kDa isoforms promote replication, while the 23- and 19-kDa isoforms suppress replication in ECs, in CD34(+) HPCs, and in huNSG mice. The role of the 25-kDa isoform is context dependent and influences the activity of the other isoforms. These isoforms localize throughout the secretory pathway, and loss of the 33- and 26-kDa UL136 isoforms results in virus maturation defects in ECs. This work reveals an intriguing functional interplay between protein isoforms that impacts virus replication, latency, and dissemination, contributing to the overall role of the UL133/8 locus in HCMV infection.

IMPORTANCE: The persistence of DNA viruses, and particularly of herpesviruses, remains an enigma because we have not completely defined the viral and host factors important to persistence. Human cytomegalovirus, a herpesvirus, persists in the absence of disease in immunocompetent individuals but poses a serious disease threat to transplant patients and the developing fetus. There is no vaccine, and current therapies do not target latent reservoirs. In an effort to define the viral factors important to persistence, we have studied viral genes with no known viral replication function in contexts important to HCMV persistence. Using models relevant to viral persistence, we demonstrate opposing roles of protein isoforms encoded by the UL136 gene in regulating latent and replicative states of infection. Our findings reveal an intriguing interplay between UL136 protein isoforms and define UL136 as an important regulator of HCMV persistence.

Cedars, A. M., Stefanescu Schmidt, A., Broberg, C., Zaidi, A., Opotowsky, A., Grewal, J., et al. (2016).

Adult congenital heart disease patients experience similar symptoms of disease activity.

Circulation.Cardiovascular Quality and Outcomes, 9(2), 161-170.

BACKGROUND: There is a lack of objective data on the symptoms characterizing disease activity among adults with congenital heart disease (ACHD). The purpose of this study was to elicit the most important symptoms from patients across the spectrum of ACHD and to examine whether reported symptoms were similar across the spectrum of ACHD as a foundation for creating a patient-reported outcome measure(s). METHODS AND RESULTS: We constructed a 39-item survey using input from physicians specializing in ACHD to assess the symptoms patients associate with disease activity. Patients (n=124) prospectively completed this survey, and the results were analyzed based on underlying anatomy and disease complexity. A confirmatory cohort of patients (n=40) was then recruited prospectively to confirm the validity of the initial data. When grouped based on underlying anatomy, significant differences in disease-related symptom rankings were found for only 6 of 39 symptoms. Six symptoms were identified which were of particular significance to patients, regardless of underlying anatomy. Patients with anatomy of great complexity experienced greater overall symptom severity than those with anatomy of low or moderate complexity, attributable exclusively to higher ranking of 5 symptoms. The second patient cohort had symptom experiences similar to those of the initial cohort, differing in only 5 of 39 symptoms. CONCLUSIONS: This study identified 6 symptoms relevant to patients across the spectrum of ACHD and remarkable homogeneity of patient experience, suggesting that a single disease-specific patient-reported outcome can be created for quality and outcome assessments.

Cefalu, W. T., Boulton, A. J. M., Tamborlane, W. V., Moses, R. G., Leroith, D., Greene, E. L., et al.

(2015). Status of diabetes care: New challenges, new concepts, new measures - focusing on the future! *Diabetes Care*, 38(7), 1177-1180.

Chandran, R., Gardiner, S. K., Fenske, T. S., & Spurgeon, E. S. (2016). Survival trends in T cell

prolymphocytic leukemia: A SEER database analysis. *Leukemia and Lymphoma*, 57(4), 942-944.

Chatzi, C., Zhang, Y., Shen, R., Westbrook, G. L., & Goodman, R. H. (2016). Transcriptional profiling of newly generated dentate granule cells using TU tagging reveals pattern shifts in gene expression during circuit integration. *Eneuro*, 3(1), 10.1523/ENEURO.0024-16.2016. eCollection 2016 Jan-Feb.

Despite representing only a small fraction of hippocampal granule cells, adult-generated newborn granule cells have been implicated in learning and memory (Aimone et al., 2011). Newborn granule cells undergo functional maturation and circuit integration over a period of weeks. However, it is difficult to assess the accompanying gene expression profiles in vivo with high spatial and temporal resolution using traditional methods. Here we used a novel method ["thiouracil (TU) tagging"] to map the profiles of nascent mRNAs in mouse immature newborn granule cells compared with mature granule cells. We targeted a nonmammalian uracil salvage enzyme, uracil phosphoribosyltransferase, to newborn neurons and mature granule cells using retroviral and lentiviral constructs, respectively. Subsequent injection of 4-TU tagged nascent RNAs for analysis by RNA sequencing. Several hundred genes were significantly enhanced in the retroviral dataset compared with the lentiviral dataset. We compared a selection of the enriched genes with steady-state levels of mRNAs using quantitative PCR. Ontology analysis revealed distinct patterns of nascent mRNA expression, with newly generated immature neurons showing enhanced expression for genes involved in synaptic function, and neural differentiation and development, as well as genes not previously associated with granule cell maturation. Surprisingly, the nascent mRNAs enriched in mature cells were related to energy homeostasis and metabolism, presumably indicative of the increased energy demands of synaptic transmission and their complex dendritic architecture. The high spatial and temporal resolution of our modified TU-tagging method provides a foundation for comparison with steady-state RNA analyses by traditional transcriptomic approaches in defining the functional roles of newborn neurons.

Chen, M., Peters, A., Huang, T., & Nan, X. (2016). Ras dimer formation as a new signaling mechanism and potential cancer therapeutic target. *Mini-Reviews in Medicinal Chemistry*, 16(5), 391-403. The K-, N-, and HRas small GTPases are key regulators of cell physiology and are frequently mutated in human cancers. Despite intensive research, previous efforts to target hyperactive Ras based on known mechanisms of Ras signaling have been met with little success. Several studies

have provided compelling evidence for the existence and biological relevance of Ras dimers, establishing a new mechanism for regulating Ras activity in cells additionally to GTP-loading and membrane localization. Existing data also start to reveal how Ras proteins dimerize on the membrane. We propose a dimer model to describe Ras-mediated effector activation, which contrasts existing models of Ras signaling as a monomer or as a 5-8 membered multimer. We also discuss potential implications of this model in both basic and translational Ras biology. © 2016 Bentham Science Publishers.

Chen, Y., Chen, Z., & Mori, M. (2016). A new statistical decision rule for single-arm phase II oncology trials. *Statistical Methods in Medical Research*, 25(1), 118-132.

Most single-arm phase II clinical trials compare the efficacy of a new treatment with historical controls through statistical hypothesis testing. One major problem with such a comparison is that the efficacy of the historical control is treated as a known constant, whereas in reality, it is never precisely known. This partially explains why many "Go" decisions made in single-arm phase II trials are shown to be incorrect in phase III trials. In this paper, we propose a new decision rule for an improved transitional decision for single-arm phase II oncology clinical trials with binary endpoints. This new decision rule is jointly based on the p value and a new statistical index named the testing confidence value. The testing confidence value reflects the uncertainty associated with the null value in the hypothesis testing of single-arm trials. Simulations are used to evaluate the operating characteristics of the new decision rule in comparison with the traditional decision rule and a widely used Bayesian decision rule. The application of the new decision rule is illustrated using a clinical trial on marginally resectable pancreatic cancer. A webpage <http://www.yiyichenbiostatistics.com/TCV.HTML> is available for readers to interactively compute the testing confidence value and to find the suggested decision based on the new decision rule. © SAGE Publications 2012.

Chen, Y., Sagar, V., Len, H. -, Peterson, K., Fan, J., Mishra, S., et al. (2016). $\hat{\text{I}}^3$ -Crystallins of the chicken lens: Remnants of an ancient vertebrate gene family in birds. *FEBS Journal*, $\hat{\text{I}}^3$ -Crystallins, abundant proteins of vertebrate lenses, were thought to be absent from birds. However, bird genomes contain well-conserved genes for $\hat{\text{I}}^3\text{S}$ - and $\hat{\text{I}}^3\text{N}$ -crystallins. Although

expressed sequence tag analysis of chicken eye found no transcripts for these genes, RT-PCR detected spliced transcripts for both genes in chicken lens, with lower levels in cornea and retina/retinal pigment epithelium. The level of mRNA for β -crystallin in chicken lens was relatively very low even though the chicken β -crystallin gene promoter had lens-preferred activity similar to that of mouse. Chicken β -crystallin was detected by a peptide antibody in lens, but not in other ocular tissues. Low levels of β -crystallin and γ -crystallin proteins were detected in chicken lens by shotgun mass spectroscopy. Water-soluble and water-insoluble lens fractions were analyzed and 1934 proteins (< 1% false discovery rate) were detected, increasing the known chicken lens proteome 30-fold. Although chicken β -crystallin is well conserved in protein sequence, it has one notable difference in leucine 16, replacing a surface glutamine conserved in other β -crystallins, possibly affecting solubility. However, L16 and engineered Q16 versions were both highly soluble and had indistinguishable circular dichroism, tryptophan fluorescence and heat stability (melting temperature $T_m \sim 65^\circ\text{C}$) profiles. L16 has been present in birds for over 100 million years and may have been adopted for a specific protein interaction in the bird lens. However, evolution has clearly reduced or eliminated expression of ancestral β -crystallins in bird lenses. The conservation of genes for β - and γ -crystallins suggests they may have been preserved for reasons unrelated to the bulk properties of the lens. © 2016 Federation of European Biochemical Societies.

Chen, Y. -, Snowden, J. M., McFarland, W., & Raymond, H. F. (2016). Pre-exposure prophylaxis (PrEP) use, seroadaptation, and sexual behavior among men who have sex with men, San Francisco, 2004–2014. *AIDS and Behavior*, , 1-7.

The Food and Drug Administration approved pre-exposure prophylaxis (PrEP) to prevent HIV infection, and the Centers for Disease Control and Prevention has presented PrEP as a prevention option for groups at high risk such as men who have sex with men (MSM). Intervention data provide some information on how PrEP affects sexual behavior of MSM in trials, open label extensions, or clinics. However, it is unclear whether sexual risk and preventive behavioral patterns are changing in the population as a whole as PrEP becomes more widely available, whether due to PrEP use or other factors. We examined trends in PrEP use, numbers of condomless anal sex partners, consistent condom use, and seroadaptive strategies in San Francisco—a city which has actively promoted PrEP—using data from National HIV Behavioral

Surveillance (NHBS). NHBS recruited 1211, 383, 373, and 268 HIV-negative MSM in 2004, 2008, 2011, and 2014, respectively. PrEP use increased from zero in 2004, 2008, and 2011 to 9.6 % in 2014. The proportion of men with no condomless anal sex partners dropped from 60.6 % in 2004, to 58.2 % in 2008, to 54.2 % in 2011, to 40.2 % in 2014. Consistent condom use decreased from 36.8 % in 2004, and 30.5 % in 2008 and 2011, to 18.3 % in 2014. PrEP's introduction and scale-up enters in a pre-existing trend of decreasing condom use and increasing sexually transmitted infections among MSM which may be accelerating in recent years. While PrEP use should be scaled up as a prevention option among those who would benefit most, we believe that public health officials need to be realistic about the possibility that condom use could very well continue to decline as PrEP use increases, and to an extent that may not be directly or indirectly offset by PrEP. © 2016 Springer Science+Business Media New York

Cherala, G., Edelman, A., Dorflinger, L., & Stanczyk, F. Z. (2016). The elusive minimum threshold concentration of levonorgestrel for contraceptive efficacy. *Contraception*,

Chien, J., & Mobbs, K. E. (2016). Oregon supreme court ruling prohibits hospital from refusing a sell order. *The Journal of the American Academy of Psychiatry and the Law*, 44(1), 111-116.

In a recent decision involving a capital murder case, Oregon State Hospital v. Butts, the Oregon Supreme Court conducted a mandamus hearing to ascertain whether Oregon State Hospital (OSH) had a legal duty to comply with a Sell order from a county trial court to provide antipsychotic medications to an incompetent defendant, despite its belief, as an institution, that medication was not clinically indicated. The case is reviewed and important implications, including the court's being granted the ability to circumvent the medical decision-making process, are discussed.

Cholerton, B., Larson, E. B., Quinn, J. F., Zabetian, C. P., Mata, I. F., Keene, C. D., et al. (2016). Precision medicine: Clarity for the complexity of dementia. *American Journal of Pathology*, 186(3), 500-506.

Three key elements to precision medicine are stratification by risk, detection of pathophysiological processes as early as possible (even before clinical presentation), and alignment of mechanism of action of intervention(s) with an individual's molecular driver(s) of

disease. Used for decades in the management of some rare diseases and now gaining broad currency in cancer care, a precision medicine approach is beginning to be adapted to cognitive impairment and dementia. This review focuses on the application of precision medicine to address the clinical and biological complexity of two common neurodegenerative causes of dementia: Alzheimer disease and Parkinson disease. © Copyright 2016 American Society for Investigative Pathology. Published by Elsevier Inc. All rights reserved.

Chou, R., Dana, T., Bougatsos, C., Grusing, S., & Blazina, I. (2016). Screening for impaired visual acuity in older adults: Updated evidence report and systematic review for the US preventive services task force. *Jama*, *315*(9), 915-933.

IMPORTANCE: Impaired visual acuity is common among older adults and can adversely affect function and quality of life. **OBJECTIVE:** To update a 2009 systematic review on screening for impaired visual acuity among older adults for the US Preventive Services Task Force (USPSTF). **DATA SOURCES:** Ovid MEDLINE (2008 to January 2016), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. **STUDY SELECTION:** Randomized clinical trials of screening; diagnostic accuracy studies of screening tests in primary care settings; and randomized clinical trials of treatment vs placebo or no treatment for uncorrected refractive errors, cataracts, and dry (atrophic) or wet (exudative) age-related macular degeneration (AMD). Studies of screening and diagnostic accuracy were limited to asymptomatic adults 65 years or older; studies of treatment included asymptomatic adults of any age. **DATA EXTRACTION AND SYNTHESIS:** One investigator abstracted data, a second checked data for accuracy, and 2 investigators independently assessed study quality using predefined criteria. Random-effects meta-analysis was used to estimate the relative and absolute benefits of vascular endothelial growth factor inhibitors (anti-VEGF) for wet AMD. **MAIN OUTCOMES AND MEASURES:** Visual acuity, vision-related function, functional capacity, harms, and diagnostic accuracy. **RESULTS:** Three trials (n = 4728) from the 2009 USPSTF review found that screening for impaired visual acuity was not associated with improved visual or clinical outcomes. In 1 good-quality trial (n = 3346), universal screening identified 27% of persons with impaired visual acuity and correctable impairment vs 3.1% with targeted screening, but there was no difference in the likelihood of visual acuity worse than 20/60 after 3 to 5 years (37% vs 35%; relative risk [RR], 1.07; 95% CI,

0.84-1.36). The 2009 review found that effective treatments are available for uncorrected refractive errors and cataracts. Ten-year trial results of dry AMD found an antioxidant/zinc combination was associated with decreased risk of visual acuity loss (46% vs 54%; odds ratio, 0.71; 95% CI, 0.57-0.88). An updated meta-analysis found anti-VEGF for wet AMD was associated with greater likelihood of having vision 20/200 or better vs sham injection (4 trials; RR, 1.47; 95% CI, 1.30-1.66; I² = 42%; absolute risk difference, 24%; 95% CI, 12%-37% after 1 year). New evidence on the diagnostic accuracy of visual acuity screening tests was limited and consistent with previous findings that screening questions or a visual acuity test was associated with suboptimal accuracy. CONCLUSIONS AND RELEVANCE: Screening can identify persons with impaired visual acuity, and effective treatments are available for common causes of impaired visual acuity, such as uncorrected refractive error, cataracts, and dry or wet AMD. However, direct evidence found no significant difference between vision screening in older adults in primary care settings vs no screening for improving visual acuity or other clinical outcomes.

Christiansen, J. S., Backeljauw, P., Bidlingmaier, M., Biller, B., Boguszewski, M., Casanueva, F. F., et al. (2016). Growth hormone research society perspective on the development of long-acting growth hormone preparations. *European Journal of Endocrinology / European Federation of Endocrine Societies*,

OBJECTIVE: The Growth Hormone (GH) Research Society convened a workshop to address important issues regarding trial design, efficacy, and safety of long-acting GH preparations (LAGH). PARTICIPANTS: A closed meeting of 55 international scientists with expertise in growth hormone, including pediatric and adult endocrinologists, basic scientists, regulatory scientists, and participants from the pharmaceutical industry. EVIDENCE: Current literature was reviewed for gaps in knowledge. Expert opinion was utilized to suggest studies required to address potential safety and efficacy issues. CONSENSUS PROCESS: Following plenary presentations summarizing the literature, breakout groups discussed questions framed by the planning committee. Attendees re-convened after each breakout session to share group reports. A writing team compiled the breakout session reports into a draft document that was discussed and revised in an open forum on the concluding day. This was edited further and then circulated to attendees from academic institutions for review after the meeting. Participants from

pharmaceutical companies did not participate in the planning, writing, or in the discussions and text revision on the final day of the workshop. Scientists from industry and regulatory agencies reviewed the manuscript to identify any factual errors. CONCLUSIONS: LAGH compounds may represent an advance over daily GH injections because of increased convenience and differing pharmacodynamic properties, providing the potential for improved adherence and outcomes. Better methods to assess adherence must be developed and validated. Long-term surveillance registries that include assessment of efficacy, cost-benefit, disease burden, quality of life, and safety are essential for understanding the impact of sustained exposure to LAGH preparations.

Cimen, H. I., Atik, Y. T., Serefoglu, E. C., & Saitz, T. R. (2016). The accuracy of references in the journal of urology. *The Journal of Urology*,

Clayburgh, D. R., Byrd, J. K., Bonfili, J., & Duvvuri, U. (2016). Intraoperative ultrasonography during transoral robotic surgery. *The Annals of Otology, Rhinology, and Laryngology*, 125(1), 37-42.

OBJECTIVE: This study describes the potential application of intraoperative ultrasound imaging during transoral robotic surgery (TORS). METHODS: Ultrasound imaging was performed during transoral robotic resection of oropharyngeal tumors in 10 patients at a tertiary academic center.

Ultrasound imaging was utilized to identify large-caliber vessels adjacent to the surgical site.

Measurements were also taken on the ultrasound of tumor thickness to determine the deep margin. Following resection, the tumor was sectioned, and a gross measurement of the tumor thickness was obtained. RESULTS: Intraoperative ultrasound use led to the identification of larger-caliber blood vessels within the operative field prior to encountering them visually.

Ultrasound could also aid in defining deep tumor margins; the tumor thickness measured via ultrasound was found to be accurate within 1 to 2 mm of the grossly measured tumor thickness.

This allowed for focused, careful dissection to protect and avoid blood vessels during dissection as well as improved tumor resection. CONCLUSIONS: The use of intraoperative ultrasound provides additional information to the head and neck surgeon during TORS. This may be used to identify blood vessels and assess tumor margins, thereby improving the safety and efficacy of TORS.

Cloyes, K. G., Rosenkranz, S. J., Berry, P. H., Supiano, K. P., Routt, M., Shannon-Dorcy, K., et al.

(2016). Essential elements of an effective prison hospice program. *American Journal of Hospice*

and Palliative Medicine, 33(4), 390-402.

As the number of prison inmates facing end-stage chronic illness grows, more prisons across the U.S. must address the need for end-of-life care. Many will likely need to develop a plan with potentially limited resources and external support. This case study presents one long-running model of care, the Louisiana State Penitentiary Prison Hospice Program. Based on field observations and in-depth interviews with hospice staff, inmate volunteers and corrections officers, we identify five essential elements that have contributed to the long-term operation of this program: patient-centered care, an inmate volunteer model, safety and security, shared values, and teamwork. We describe key characteristics of each of these elements, discuss how they align with earlier recommendations and research, and show how their integration supports a sustained model of prison end-of-life care. © 2015, © The Author(s) 2015.

Cohen, D. M. (2016). Modeling the neurologic and cognitive effects of hyponatremia. *Journal of the American Society of Nephrology, 27(3), 659-661.*

Collin, P., Laubster, E., Denard, P. J., Akue, F. A., & Ladermann, A. (2016). The nice knot as an improvement on current knot options: A mechanical analysis. *Orthopaedics & Traumatology, Surgery & Research : OTSR,*

PURPOSE: There is currently a wide range of suture knots used in rotator cuff repair. The purpose of this study was to compare a new type of self-locking sliding knot called the Nice knot to the self-locking and sliding Nicky's knot. METHODS: Nice knots and Nicky's knots were tied and subjected to mechanical testing including a pure traction stress and a series of dynamic stresses. Both knots were tied using standard braided suture and reinforced braided suture. The responses to these stresses were measured in the amount of elongation of the knot, maximum effort needed for failure, stiffness of construct and dynamic stiffness. RESULTS: With both knots the standard suture had a lower amount of elongation during the dynamic tests than the reinforced braided suture. The reinforced braided suture showed superior results during maximal effort in the pure traction tests. An increased failure rate occurred due to elongation when a dynamic stress was applied to the reinforced suture in both knot types. During dynamic testing the Nice knot showed a decrease in the amount of elongation ($P < 0.001$). CONCLUSIONS: The Nice knot

provides a sliding locking knot option which can decrease the risk of elongation during dynamic stress. LEVEL OF EVIDENCE: Basic Science Study, Biomechanical Study.

Connelly, C. R., Kemp Bohan, P. M., Cook, M. R., Moren, A. M., Schreiber, M. A., & Kiraly, L. N.

(2016). A night float week in a surgical clerkship improves student team cohesion. *American Journal of Surgery*,

BACKGROUND: We hypothesize that night float rotations in the third-year surgical clerkship improve student learning and perceptions of team cohesion. METHODS: A 1-week night float (NF) system was implemented during the 2013 to 2014 academic year for students. Each student completed 1 week of NF with the Trauma/Emergency General Surgery service. The Perceived Cohesion Scale survey was prospectively administered and National Board of Medical Examiners academic performance retrospectively reviewed. RESULTS: We surveyed 70 medical students, 37 traditional call and 33 NF students, with 91% response rate. Perception of team cohesion increased significantly, without perceived loss of educational benefit. Examination scores increased significantly comparing pre- and postintervention groups, with this trend continuing in the following academic year. CONCLUSIONS: A week-long student NF experience significantly improved perception of team cohesion and standardized examination results. A dedicated period of NF during the surgical clerkship may improve its overall educational value.

Cooper, T. M., Cassar, J., Eckroth, E., Malvar, J., Sposto, R., Gaynon, P., et al. (2016). A phase I

study of quizartinib combined with chemotherapy in relapsed childhood leukemia: A therapeutic advances in childhood leukemia & lymphoma (TACL) study. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,

PURPOSE: To determine a safe and biologically active dose of quizartinib (AC220), a potent and selective class III receptor tyrosine kinase (RTK) FLT3 inhibitor, in combination with salvage chemotherapy in children with relapsed acute leukemia. EXPERIMENTAL DESIGN: Quizartinib was administered orally to children with relapsed AML or MLL-rearranged ALL following 5 days of high dose cytarabine and etoposide (AE). A 3+3 dose escalation design was used to identify a safe and biologically active dose. Plasma inhibitory assay (PIA) testing was performed weekly to determine biologic activity. RESULTS: Toxicities were consistent with intensive relapsed leukemia

regimens. One of 6 patients experienced a dose-limiting toxicity (DLT) at 40 mg/m²/day (elevated lipase) and 1 of 9 had a DLT (hyperbilirubinemia) at the highest tested dose of 60 mg/m²/day. Of 17 response evaluable patients, 2 had complete response (CR), 1 complete response without platelet recovery (CRp), 1 complete response with incomplete neutrophil and platelet recovery (CRI), 10 stable disease (SD), and 3 progressive disease (PD). Of 7 FLT3-ITD patients, 1 achieved CR, 1 CRp, 1 CRI and 4 SD. FLT3-ITD patients, but not FLT3-wild type (WT) patients, had significantly lower blast counts post-quizartinib. FLT3 phosphorylation was completely inhibited in all patients. CONCLUSIONS: Quizartinib plus intensive chemotherapy is well tolerated at 60 mg/m²/day with near complete inhibition of FLT3 phosphorylation in all patients. The favorable toxicity profile, pharmacodynamic activity and encouraging response rates warrant further testing of quizartinib in children with FLT3-ITD AML.

Coronado, G. D., Retecki, S., Schneider, J., Taplin, S. H., Burdick, T., & Green, B. B. (2016).

Recruiting community health centers into pragmatic research: Findings from STOP CRC. *Clinical Trials*, 13(2), 214-222.

Background: Challenges of recruiting participants into pragmatic trials, particularly at the level of the health system, remain largely unexplored. As part of Strategies and Opportunities to STOP Colon Cancer in Priority Populations (STOP CRC), we recruited eight separate community health centers (consisting of 26 individual safety net clinics) into a large comparative effectiveness pragmatic study to evaluate methods of raising the rates of colorectal cancer screening. Methods: In partnership with STOP CRC's advisory board, we defined criteria to identify eligible health centers and applied these criteria to a list of health centers in Washington, Oregon, and California affiliated with Oregon Community Health Information Network, a 16-state practice-based research network of federally sponsored health centers. Project staff contacted centers that met eligibility criteria and arranged in-person meetings of key study investigators with health center leadership teams. We used the Consolidated Framework for Implementation Research to thematically analyze the content of discussions during these meetings to identify major facilitators of and barriers to health center participation. Results: From an initial list of 41 health centers, 11 met the initial inclusion criteria. Of these, leaders at three centers declined and at eight centers (26 clinic sites) agreed to participate (73%). Participating and nonparticipating

health centers were similar with respect to clinic size, percent Hispanic patients, and percent uninsured patients. Participating health centers had higher proportions of Medicaid patients and higher baseline colorectal cancer screening rates. Common facilitators of participation were perception by center leadership that the project was an opportunity to increase colorectal cancer screening rates and to use electronic health record tools for population management. Barriers to participation were concerns of center leaders about ability to provide fecal testing to and assure follow-up of uninsured patients, limited clinic capacity to prepare mailings required by the study protocol, discomfort with randomization, and concerns about delaying program implementation at some clinics due to the research requirements. Conclusion: Our findings address an important research gap and may inform future efforts to recruit community health centers into pragmatic research. © The Author(s) 2015.

Council, M. L., Alam, M., Gloster, H. M., J., Bordeaux, J. S., Carroll, B. T., Leitenberger, J. J., et al.

(2016). Identifying and defining complications of dermatologic surgery to be tracked in the American college of Mohs surgery (ACMS) registry. *Journal of the American Academy of Dermatology*, 74(4), 739-745.

Background In recent years, increasing emphasis has been placed on value-based health care delivery. Dermatology must develop performance measures to judge the quality of services provided. The implementation of a national complication registry is one such method of tracking surgical outcomes and monitoring the safety of the specialty. **Objective** The purpose of this study was to define critical outcome measures to be included in the complications registry of the American College of Mohs Surgery (ACMS). **Methods** A Delphi process was used to reach consensus on the complications to be recorded. **Results** Four major and one minor complications were selected: death, bleeding requiring additional intervention, functional loss attributable to surgery, hospitalization for an operative complication, and surgical site infection. **Limitations** This article addresses only one aspect of registry development: identifying and defining surgical complications. **Conclusion** The ACMS Registry aims to gather data to monitor the safety and value of dermatologic surgery. Determining and defining the outcomes to be included in the registry is an important foundation toward this endeavor. © 2015 American Academy of Dermatology, Inc.

Cox, D. R., Ashby, S., DeConde, A. S., Mace, J. C., Orlandi, R. R., Smith, T. L., et al. (2016). Dyad of pain and depression in chronic rhinosinusitis. *International Forum of Allergy & Rhinology*, 6(3), 308-314.

BACKGROUND: Pain and depression often coexist as comorbidities in patients with chronic disease and exert a major impact on quality of life (QOL). Little is known about the relationship between pain and depression in chronic rhinosinusitis (CRS). Our objective was to investigate this relationship and to analyze the effect of pain and depression on QOL in CRS. **METHODS:** Patients with CRS were prospectively recruited as part of an observational cohort study. A total of 70 participants provided pain scores using both the Brief Pain Inventory Short Form (BPI-SF) and the Short Form McGill Pain Questionnaire (SF-MPQ). Patients at risk for depression were identified using the Patient Health Questionnaire-2 (PHQ-2). CRS-specific QOL was determined using the 22-item Sino-Nasal Outcome Test (SNOT-22). **RESULTS:** Significant positive correlations were found between depression scores and all pain measures ($R = 0.475$ to 0.644 , $p \leq 0.05$) had significantly higher scores on all reported pain measures. Significant positive correlations were found between all pain measures, the total SNOT-22 score, and 3 SNOT-22 subdomains (sleep, psychological dysfunction, and ear/facial symptoms; $R = 0.323$ to 0.608 , $p < 0.05$).

CONCLUSION: Adult patients with CRS at risk for depression experience more pain and have overall worse disease-specific QOL. Further research investigating the complex interactions between depression and pain and the role it plays in CRS disease-specific QOL is warranted.

Cozzoli, D. K., Courson, J., Rostock, C., Campbell, R. R., Wroten, M. G., McGregor, H., et al. (2016).

Protein kinase C epsilon activity in the nucleus accumbens and central nucleus of the amygdala mediates binge alcohol consumption. *Biological Psychiatry*, 79(6), 443-451.

background Protein kinase C epsilon (PKC ϵ) is emerging as a potential target for the development of pharmacotherapies to treat alcohol use disorders, yet little is known regarding how a history of a highly prevalent form of drinking, binge alcohol intake, influences enzyme priming or the functional relevance of kinase activity for excessive alcohol intake. **Methods** Immunoblotting was employed on tissue from subregions of the nucleus accumbens (NAc) and the amygdala to examine both idiopathic and binge drinking-induced changes in constitutive PKC ϵ priming. The functional relevance of PKC ϵ translocation for binge drinking and determination of potential

upstream signaling pathways involved were investigated using neuropharmacologic approaches within the context of two distinct binge drinking procedures, drinking in the dark and scheduled high alcohol consumption. Results Binge alcohol drinking elevated p(Ser729)-PKC ϵ levels in both the NAc and the central nucleus of the amygdala (CeA). Moreover, immunoblotting studies of selectively bred and transgenic mouse lines revealed a positive correlation between the propensity to binge drink alcohol and constitutive p(Ser729)-PKC ϵ levels in the NAc and CeA. Finally, neuropharmacologic inhibition of PKC ϵ translocation within both regions reduced binge alcohol consumption in a manner requiring intact group 1 metabotropic glutamate receptors, Homer2, phospholipase C, and/or phosphatidylinositol-3 kinase function. Conclusions Taken together, these data indicate that PKC ϵ signaling in both the NAc and CeA is a major contributor to binge alcohol drinking and to the genetic propensity to consume excessive amounts of alcohol. © 2016 Society of Biological Psychiatry.

Crawford, J. D., Robbins, N. G., Harry, L. A., Wilson, D. G., McLafferty, R. B., Mitchell, E. L., et al. (2016). Characterization of tibial velocities by duplex ultrasound in severe peripheral arterial disease and controls presented as an oral presentation at the 2015 vascular annual meeting of the society for vascular surgery, chicago, ill, june 17-20, 2015. *Journal of Vascular Surgery*, 63(3), 646-651.

Background The relationship between tibiopopliteal velocities and peripheral arterial disease (PAD) severity is not well understood. We sought to characterize tibiopopliteal velocities in severe PAD and non-PAD control patients. Methods Patients with an arterial duplex ultrasound (DUS) examination with PAD evaluated during a 5-year period were retrospectively compared with non-PAD controls. Control DUS examinations were collected sequentially during a 6-month period, retrospectively. PAD patients included those with lifestyle-limiting intermittent claudication warranting revascularization and patients with critical limb ischemia, defined as ischemic rest pain, gangrene, or a nonhealing ischemic ulcer. For each, tibial and popliteal artery peak systolic velocity (PSV) was measured at the proximal, mid, and distal segment of each artery, and a mean PSV for each artery was calculated. Mean PSV, ankle-brachial indices, peak ankle velocity (PAV), average ankle velocity (AAV), mean tibial velocity (MTV), and ankle-profunda index (API) were compared between the two groups using independent t-tests. PAV is the maximum PSV of

the distal peroneal, posterior tibial (PT), or anterior tibial (AT) artery; AAV is the average PSV of the distal peroneal, PT, and AT arteries; MTV is calculated by first averaging the proximal, mid, and distal PSV for each tibial artery and then averaging the three means together; API is the AAV divided by proximal PSV of the profunda. Results DUS was available in 103 patients with PAD (68 patients with critical limb ischemia and 35 patients with intermittent claudication) and 68 controls. Mean ankle-brachial index in the PAD group was 0.64 ± 0.25 compared with 1.08 ± 0.09 in controls ($P = .006$). Mean PSVs were significantly lower in PAD patients than in controls at the popliteal (64.6 ± 42.2 vs 76.2 ± 29.6 ; $P = .037$), peroneal (34.3 ± 26.4 vs 53.8 ± 23.3 ; $P < .001$), AT (43.7 ± 31.4 vs 65.4 ± 25.0 ; $P < .001$), and PT (43.4 ± 42.3 vs 74.1 ± 30.6 ; $P < .001$) and higher at the profunda (131.5 ± 88.0 vs 96.2 ± 44.8 ; $P = .001$). Tibial parameters including PAV (52.6 ± 45.0 vs 86.9 ± 35.7 ; $P < .001$), AAV (37.4 ± 26.4 vs 64.5 ± 21.7 ; $P < .001$), MTV (41.7 ± 30.4 vs 65.4 ± 21.7 ; $P < .001$), and API (0.43 ± 0.45 vs 0.75 ± 0.30 ; $P < .001$) were significantly lower in the PAD group than in controls.

Nonoverlapping 95% confidence interval reference ranges were established for severe PAD and non-PAD controls. Conclusions This study aims to characterize lower extremity arterial PSVs and ankle parameters in severe PAD and non-PAD controls. These early criteria establish reference ranges to guide vascular laboratory interpretation and clinical decision-making. © 2016 Society for Vascular Surgery.

Cunningham, A., Frazier, D., Marriage, B., Mofidi, S., Ogata, B., Rohr, F., et al. (2016). Role of medical food in MMA. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, 18(4), 413-414.

Dailey, R. A., Marx, D. P., & Ahn, E. S. (2015). Porcine dermal collagen in lower eyelid retraction repair. *Ophthalmic Plastic and Reconstructive Surgery*, 31(3), 233-241.

PURPOSE: To describe clinical outcomes of patients receiving porcine dermal matrix implants for lower eyelid retraction repair. METHODS: A retrospective review of all patients who underwent lower eyelid retraction repair with porcine dermal matrix implantation between June 2007 and July 2013 at a tertiary care center was conducted. Patient demographics, procedure(s) performed, preoperative and postoperative marginal reflex distance, inferior scleral show, and

complications were reviewed. Patients with a prior history of lower eyelid surgery were excluded. The study is Health Insurance Portability and Accountability Act compliant, institutional review board approved, and adherent to the Declaration of Helsinki. RESULTS: One hundred patients (160 eyelids) received porcine dermal collagen implants. Fifty-six patients had thyroid eye disease, 23 had midface descent, 10 had seventh nerve palsies, and 11 had other etiologies of retraction. The average preoperative marginal reflex distance was 7.64 mm in the OD and 7.17 mm in the OS, compared with 6.40 mm in the OD and 6.22 mm in the OS postoperatively. The average preoperative inferior scleral show was 2.04 in the OD and 1.70 in the OS compared with 0.81 mm in the OD and 0.65 mm in the OS postoperatively. Follow up ranged from 1.46 to 66.04 months, with an average of 14.06 months and median of 8.84 months. Nineteen eyelids had implant-related complications: 7 with cyst formation, 7 with exposure/rejection, 2 with long-term pain, 2 with transient inflammation, and 3 with irregular implant contour. CONCLUSIONS: Porcine dermal matrix implants provide reliable support, integration, and function in lower eyelid retraction repair without significant resorption or complications in the majority of patients.

Daniels, A. H., Kawaguchi, S., Contag, A. G., Rastegar, F., Waagmeester, G., Anderson, P. A., et al. (2016). Hospital charges associated with "never events": Comparison of anterior cervical discectomy and fusion, posterior lumbar interbody fusion, and lumbar laminectomy to total joint arthroplasty. *Journal of Neurosurgery.Spine*, , 1-5.

OBJECTIVE Beginning in 2008, the Centers for Medicare and Medicaid Service (CMS) determined that certain hospital-acquired adverse events such as surgical site infection (SSI) following spine surgery should never occur. The following year, they expanded the ruling to include deep vein thrombosis (DVT) and pulmonary embolism (PE) following total joint arthroplasty. Due to their ruling that "never events" are not the payers' responsibility, CMS insists that the costs of managing these complications be borne by hospitals and health care providers, rather than billings to health care payers for additional care required in their management. Data comparing the expected costs of such adverse events in patients undergoing spine and orthopedic surgery have not previously been reported. METHODS The California State Inpatient Database (CA-SID) from 2008 to 2009 was used for the analysis. All patients with primary procedure codes indicating anterior cervical discectomy and fusion (ACDF), posterior lumbar interbody fusion (PLIF), lumbar

laminectomy (LL), total knee replacement (TKR), and total hip replacement (THR) were analyzed. Patients with diagnostic and/or treatment codes for DVT, PE, and SSI were separated from patients without these complication codes. Patients with more than 1 primary procedure code or more than 1 complication code were excluded. Median charges for treatment from primary surgery through 3 months postoperatively were calculated. RESULTS The incidence of the examined adverse events was lowest for ACDF (0.6% DVT, 0.1% PE, and 0.03% SSI) and highest for TKA (1.3% DVT, 0.3% PE, 0.6% SSI). Median inpatient charges for uncomplicated LL was \$51,817, compared with \$73,432 for ACDF, \$143,601 for PLIF, \$74,459 for THR, and \$70,116 for TKR. Charges for patients with DVT ranged from \$108,387 for TKR (1.5 times greater than index) to \$313,536 for ACDF (4.3 times greater than index). Charges for patients with PE ranged from \$127,958 for TKR (1.8 times greater than index) to \$246,637 for PLIF (1.7 times greater than index). Charges for patients with SSI ranged from \$168,964 for TKR (2.4 times greater than index) to \$385,753 for PLIF (2.7 times greater than index). CONCLUSIONS Although incidence rates are low, adverse events of spinal procedures substantially increase the cost of care. Charges for patients experiencing DVT, PE, and SSI increased in this study by factors ranging from 1.8 to 4.3 times those for patients without such complications across 5 common spinal and orthopedic procedures. Cost projections by health care providers will need to incorporate expected costs of added care for patients experiencing such complications, assuming that the cost burden of such events continues to shift from payers to providers.

De Gauna, S. R., González-Otero, D. M., Ruiz, J., & Russell, J. K. (2016). Feedback on the rate and depth of chest compressions during cardiopulmonary resuscitation using only accelerometers. *Plos One*, 11(3)

Background: Quality of cardiopulmonary resuscitation (CPR) is key to increase survival from cardiac arrest. Providing chest compressions with adequate rate and depth is difficult even for welltrained rescuers. The use of real-time feedback devices is intended to contribute to enhance chest compression quality. These devices are typically based on the double integration of the acceleration to obtain the chest displacement during compressions. The integration process is inherently unstable and leads to important errors unless boundary conditions are applied for each compression cycle. Commercial solutions use additional reference signals to establish these

conditions, requiring additional sensors. Our aim was to study the accuracy of three methods based solely on the acceleration signal to provide feedback on the compression rate and depth. Materials and Methods: We simulated a CPR scenario with several volunteers grouped in couples providing chest compressions on a resuscitation manikin. Different target rates (80, 100, 120, and 140 compressions per minute) and a target depth of at least 50 mm were indicated. The manikin was equipped with a displacement sensor. The accelerometer was placed between the rescuer's hands and the manikin's chest. We designed three alternatives to direct integration based on different principles (linear filtering, analysis of velocity, and spectral analysis of acceleration). We evaluated their accuracy by comparing the estimated depth and rate with the values obtained from the reference displacement sensor. Results: The median (IQR) percent error was 5.9% (2.8-10.3), 6.3% (2.9-11.3), and 2.5% (1.2-4.4) for depth and 1.7% (0.0-2.3), 0.0% (0.0-2.0), and 0.9% (0.4-1.6) for rate, respectively. Depth accuracy depended on the target rate ($p < 0.001$) and on the rescuer couple ($p < 0.001$) within each method. Conclusions: Accurate feedback on chest compression depth and rate during CPR is possible using exclusively the chest acceleration signal. The algorithm based on spectral analysis showed the best performance. Despite these encouraging results, further research should be conducted to assess the performance of these algorithms with clinical data. © 2016 Ruiz de Gauna et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

de Melo Campos, P., Machado-Neto, J. A., Eide, C. A., Savage, S. L., Scopim-Ribeiro, R., da Silva Souza Duarte, A., et al. (2015). IRS2 silencing increases apoptosis and potentiates the effects of ruxolitinib in JAK2V617F-positive myeloproliferative neoplasms. *Oncotarget*, 7(6), 6948-6959. The recurrent V617F mutation in JAK2 (JAK2V617F) has emerged as the primary contributor to the pathogenesis of myeloproliferative neoplasms (MPN). However, the lack of complete response in most patients treated with the JAK1/2 inhibitor, ruxolitinib, indicates the need for identifying pathways that cooperate with JAK2. Activated JAK2 was found to be associated with the insulin receptor substrate 2 (IRS2) in non-hematological cells. We identified JAK2/IRS2 binding in JAK2V617F HEL cells, but not in the JAK2WT U937 cell line. In HEL cells, IRS2 silencing

decreased STAT5 phosphorylation, reduced cell viability and increased apoptosis; these effects were enhanced when IRS2 silencing was combined with ruxolitinib. In U937 cells, IRS2 silencing neither reduced cell viability nor induced apoptosis. IRS1/2 pharmacological inhibition in primary MPN samples reduced cell viability in JAK2V617F-positive but not JAK2WT specimens; combination with ruxolitinib had additive effects. IRS2 expression was significantly higher in CD34+ cells from essential thrombocythemia patients compared to healthy donors, and in JAK2V617F MPN patients when compared to JAK2WT. Our data indicate that IRS2 is a binding partner of JAK2V617F in MPN. IRS2 contributes to increased cell viability and reduced apoptosis in JAK2-mutated cells. Combined pharmacological inhibition of IRS2 and JAK2 may have a potential clinical application in MPN.

de Vries, Y. A., de Jonge, P., van den Heuvel, E., Turner, E. H., & Roest, A. M. (2016). Influence of baseline severity on antidepressant efficacy for anxiety disorders: Meta-analysis and meta-regression. *The British Journal of Psychiatry : The Journal of Mental Science*,

BACKGROUND: Antidepressants are established first-line treatments for anxiety disorders, but it is not clear whether they are equally effective across the severity range. AIMS: To examine the influence of baseline severity of anxiety on antidepressant efficacy for generalised anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and panic disorder. METHOD: Fifty-six trials of second-generation antidepressants for the short-term treatment of an anxiety disorder were included. Baseline and change scores were extracted for placebo and treatment groups in each trial. Mixed effects meta-regression was used to investigate the effects of treatment group, baseline severity and their interaction. RESULTS: Increased baseline severity did not predict greater improvement in drug groups compared with placebo groups. Standardised regression coefficients of the interaction term between baseline severity and treatment group were 0.04 (95% CI -0.13 to 0.20, P = 0.65) for GAD, -0.06 (95% CI -0.20 to 0.09, P = 0.43) for SAD, 0.04 (95% CI -0.07 to 0.16, P = 0.46) for OCD, 0.16 (95% CI -0.22 to 0.53, P = 0.37) for PTSD and 0.002 (95% CI -0.10 to 0.10, P = 0.96) for panic disorder. For OCD, baseline severity did predict improvement in both placebo and drug groups equally (beta = 0.11, 95% CI 0.05 to 0.17, P = 0.001).

CONCLUSIONS: No relationship between baseline severity and drug-placebo difference was found

for anxiety disorders. These results suggest that if the efficacy of antidepressants is considered clinically relevant, they may be prescribed to patients with anxiety regardless of symptom severity.

Del Prete, G. Q., Oswald, K., Lara, A., Shoemaker, R., Smedley, J., Macallister, R., et al. (2016).

Elevated plasma viral loads in romidepsin-treated simian immunodeficiency virus-infected rhesus macaques on suppressive combination antiretroviral therapy. *Antimicrobial Agents and Chemotherapy*, 60(3), 1560-1572.

Replication-competent human immunodeficiency virus (HIV) persists in infected people despite suppressive combination antiretroviral therapy (cART), and it represents a major obstacle to HIV functional cure or eradication. We have developed a model of cART-mediated viral suppression in simian human immunodeficiency virus (SIV) mac239-infected Indian rhesus macaques and evaluated the impact of the histone deacetylase inhibitor (HDACi) romidepsin (RMD) on viremia in vivo. Eight macaques virologically suppressed to clinically relevant levels (>30 viral RNA copies/ml of plasma), using a three-class five-drug cART regimen, received multiple intravenous infusions of either RMD (n5) or saline (n3) starting 31 to 54 weeks after cART initiation. In vivo RMD treatment resulted in significant transient increases in acetylated histone levels in CD4T cells. RMD-treated animals demonstrated plasma viral load measurements for each 2-week treatment cycle that were significantly higher than those in saline control-treated animals during periods of treatment, suggestive of RMD-induced viral reactivation. However, plasma virus rebound was indistinguishable between RMD-treated and control-treated animals for a subset of animals released from cART. These findings suggest that HDACi drugs, such as RMD, can reactivate residual virus in the presence of suppressive antiviral therapy and may be a valuable component of a comprehensive HIV functional cure/eradication strategy. Copyright © 2016, American Society for Microbiology. All Rights Reserved.

Del Prete, G. Q., Smedley, J., Macallister, R., Jones, G. S., Li, B., Hattersley, J., et al. (2016). Short communication: Comparative evaluation of coformulated injectable combination antiretroviral therapy regimens in simian immunodeficiency virus-infected rhesus macaques. *AIDS Research and Human Retroviruses*, 32(2), 163-168.

The use of nonhuman primate (NHP) models to study persistent residual virus and viral eradication strategies in combination antiretroviral therapy (cART)-treated individuals requires regimens that effectively suppress SIV replication to clinically relevant levels in macaques. We developed and evaluated two novel cART regimens in SIVmac239-infected rhesus macaques: (1) a "triple regimen" containing the nucleo(s)tide reverse transcriptase inhibitors emtricitabine (FTC) and tenofovir disoproxil fumarate [TDF, prodrug of tenofovir (TFV, PMPA)] with the integrase strand transfer inhibitor dolutegravir (DTG) (n = 3), or (2) a "quad regimen" containing the same three drugs plus the protease inhibitor darunavir (DRV) (n = 3), with each regimen coformulated for convenient administration by a single daily subcutaneous injection. Plasma drug concentrations were consistent across animals within the triple and quad regimen-treated groups, although DTG levels were lower in the quad regimen animals. Time to achieve plasma viral loads stably <30 viral RNA copies/ml ranged from 12 to 20 weeks of treatment between animals, and viral loads <30 viral RNA copies/ml plasma were maintained through 40 weeks of follow-up on cART. Notably, although we show virologic suppression and development of viral resistance in a separate cohort of SIV-infected animals treated with oral DRV monotherapy, the addition of DRV in the quad regimen did not confer an apparent virologic benefit during early treatment, hence the quad regimen-treated animals were switched to the triple regimen after 4 weeks. This coformulated triple cART regimen can be safely, conveniently, and sustainably administered to durably suppress SIV replication to clinically relevant levels in rhesus macaques. © Copyright 2016, Mary Ann Liebert, Inc. 2016.

Deodhar, A., Mittal, M., Reilly, P., Bao, Y., Manthena, S., Anderson, J., et al. (2016). Ankylosing spondylitis diagnosis in US patients with back pain: Identifying providers involved and factors associated with rheumatology referral delay. *Clinical Rheumatology*,
This study aimed to identify providers involved in diagnosing ankylosing spondylitis (AS) following back pain diagnosis in the USA and to identify factors leading to the delay in rheumatology referrals. The Truven Health MarketScan(R) US Commercial Database was searched for patients aged 18-64 years with back pain diagnosis in a non-rheumatology setting followed by AS diagnosis in any setting during January 2000-December 2012. Patients with a rheumatologist visit on or before AS diagnosis were considered referred. Cox regression was used to determine

factors associated with referral time after adjusting for age, sex, comorbidities, physician specialty, drug therapy, and imaging procedures. Of 3336 patients included, 1244 (37 %) were referred to and diagnosed by rheumatologists; the others were diagnosed in primary care (25.7 %), chiropractic/physical therapy (7 %), orthopedic surgery (3.8 %), pain clinic (3.6 %), acute care (3.4 %), and other (19.2 %) settings. Median time from back pain diagnosis to rheumatology referral was 307 days and from first rheumatologist visit to AS diagnosis was 28 days. Referred patients were more likely to be younger (hazard ratio [HR] = 0.986; $p < 0.0001$), male (HR = 1.15; $p = 0.0163$), diagnosed with uveitis (HR = 1.49; $p = 0.0050$), referred by primary care physicians (HR = 1.96; $p < 0.0001$), prescribed non-steroidal anti-inflammatory drugs (HR = 1.55; $p < 0.0001$), disease-modifying antirheumatic drugs (HR = 1.33; $p < 0.0001$), and tumor necrosis factor inhibitors (HR = 1.40; $p = 0.0036$), and to have had spinal/pelvic X-ray prior to referral (HR = 1.28; $p = 0.0003$). During 2000-2012, most patients with AS were diagnosed outside of rheumatology practices. The delay before referral to rheumatology was 10 months; AS diagnosis generally followed within a month. Earlier referral of patients with AS signs and symptoms may lead to more timely diagnosis and appropriate treatment.

DeVoe, J. E., Bazemore, A. W., Cottrell, E. K., Likumahuwa-Ackman, S., Grandmont, J., Spach, N., et al. (2016). Perspectives in primary care: A conceptual framework and path for integrating social determinants of health into primary care practice. *Annals of Family Medicine*, 14(2), 104-108.

Devoe, J. E., Tillotson, C. J., Marino, M., O'Malley, J., Angier, H., Wallace, L. S., et al. (2016). Trends in type of health insurance coverage for US children and their parents, 1998-2011. *Academic Pediatrics*, 16(2), 192-199.

Objective To examine trends in health insurance type among US children and their parents.
Methods Using the Medical Expenditure Panel Survey (1998-2011), we linked each child ($n = 120,521$; weighted $n \hat{=} 70$ million) with his or her parent or parents and assessed patterns of full-year health insurance type, stratified by income. We examined longitudinal insurance trends using joinpoint regression and further explored these trends with adjusted regression models.
Results When comparing 1998 to 2011, the percentage of low-income families with both child

and parent or parents privately insured decreased from 29.2% to 19.1%, with an estimated decline of -0.86 (95% confidence interval, -1.10, -0.63) unadjusted percentage points per year; middle-income families experienced a drop from 74.5% to 66.3%, a yearly unadjusted percentage point decrease of -0.73 (95% confidence interval, -0.98, -0.48). The discordant pattern of publicly insured children with uninsured parents increased from 10.4% to 27.2% among low-income families and from 1.4% to 6.7% among middle-income families. Results from adjusted models were similar to joinpoint regression findings. Conclusions During the past decade, low- and middle-income US families experienced a decrease in the percentage of child-parent pairs with private health insurance and pairs without insurance. Concurrently, there was a rise in discordant coverage patterns - mainly publicly insured children with uninsured parents.

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Dixon-Ibarra, A., Driver, S., Vanderbom, K., & Humphries, K. (2016). Understanding physical activity in the group home setting: A qualitative inquiry. *Disability and Rehabilitation*, , 1-10.

PURPOSE: Persons with intellectual disabilities have low physical activity levels and high rates of chronic disease. One predictor limitedly explored is the home environment, which could influence the type and amount of physical activity in this population. The purpose of this study is to qualitatively explore physical activity in the group home setting and determine what key stakeholders want from a physical activity programme. **METHOD:** This study adopted a qualitative descriptive design, using semistructured focus groups. Twenty stakeholders (i.e., residents with intellectual disability, support staff and programme coordinators) participated in one of three focus groups, separated by stakeholder status. **RESULTS:** A number of factors emerged that would assist rehabilitation professionals in understanding physical activity within the group home setting. The following six meta-themes were identified: nature of residents' physical activity, facilitators to physical activity, barriers to physical activity, personal factors, organizational factors and solutions to increase physical activity. **CONCLUSIONS:** Findings suggest that residents with intellectual disabilities have low physical activity and opportunities for participation. Key attributes of the group home setting were identified between barriers and facilitators to activity. Consideration for the development of physical activity programmes should focus on the unique needs of the group home setting as expressed by stakeholders. Implications for rehabilitation

Physical activity can improve physical fitness, function, and community participation yet physical activity remains low among adults with intellectual disabilities. Understanding physical activity within the group home setting is essential to develop targeted interventions to increase activity within that environment. Key barriers for physical activity within the group home setting include; operational priorities, limited staff, staff turnover, busy schedules, and staff attitudes towards physical activity.

Dohare, P., Zia, M. T., Ahmed, E., Ahmed, A., Yadala, V., Schober, A. L., et al. (2016). AMPA-kainate receptor inhibition promotes neurologic recovery in premature rabbits with intraventricular hemorrhage. *Journal of Neuroscience*, 36(11), 3363-3377.

Intraventricular hemorrhage (IVH) in preterm infants leads to cerebral inflammation, reduced myelination of the white matter, and neurological deficits. No therapeutic strategy exists against the IVH-induced white matter injury. AMPA-kainate receptor induced excitotoxicity contributes to oligodendrocyte precursor cell (OPC) damage and hypomyelination in both neonatal and adult models of brain injury. Here, we hypothesized that IVH damages white matter via AMPA receptor activation, and that AMPA-kainate receptor inhibition suppresses inflammation and restores OPC maturation, myelination, and neurologic recovery in preterm newborns with IVH. We tested these hypotheses in a rabbit model of glycerol-induced IVH and evaluated the expression of AMPA receptors in autopsy samples from human preterm infants. GluR1-GluR4 expressions were comparable between preterm humans and rabbits with and without IVH. However, GluR1 and GluR2 levels were significantly lower in the embryonic white matter and germinal matrix relative to the neocortex in both infants with and without IVH. Pharmacological blockade of AMPA-kainate receptors with systemic NBQX, or selective AMPA receptor inhibition by intramuscular perampanel restored myelination and neurologic recovery in rabbits with IVH. NBQX administration also reduced the population of apoptotic OPCs, levels of several cytokines (TNF α , IL-1 α , IL-6, LIF), and the density of Iba1+ microglia in pups with IVH. Additionally, NBQX treatment inhibited STAT-3 phosphorylation, but not astrogliosis or transcription factors regulating gliosis. Our data suggest that AMPA-kainate receptor inhibition alleviates OPC loss and IVH-induced inflammation and restores myelination and neurologic recovery in preterm rabbits with IVH. Therapeutic use of

FDA-approved perampanel treatment might enhance neurologic outcome in premature infants with IVH. © 2016 the authors.

Driessnack, M. (2016). Editorial for the genetics issue. *Journal of Pediatric Nursing, 31*(1), 1-2.

Druzinsky, R. E., Balhoff, J. P., Crompton, A. W., Done, J., German, R. Z., Haendel, M. A., et al.

(2016). Muscle logic: New knowledge resource for anatomy enables comprehensive searches of the literature on the feeding muscles of mammals. *Plos One, 11*(2)

Background: In recent years large bibliographic databases have made much of the published literature of biology available for searches. However, the capabilities of the search engines integrated into these databases for text-based bibliographic searches are limited. To enable searches that deliver the results expected by comparative anatomists, an underlying logical structure known as an ontology is required. Development and Testing of the Ontology: Here we present the Mammalian Feeding Muscle Ontology (MFMO), a multi-species ontology focused on anatomical structures that participate in feeding and other oral/pharyngeal behaviors. A unique feature of the MFMO is that a simple, computable, definition of each muscle, which includes its attachments and innervation, is true across mammals. This construction mirrors the logical foundation of comparative anatomy and permits searches using language familiar to biologists. Further, it provides a template for muscles that will be useful in extending any anatomy ontology. The MFMO is developed to support the Feeding Experiments End-User Database Project (FEED, <https://feedexp.org/>), a publicly-available, online repository for physiological data collected from in vivo studies of feeding (e.g., mastication, biting, swallowing) in mammals. Currently the MFMO is integrated into FEED and also into two literature-specific implementations of Textpresso, a text-mining system that facilitates powerful searches of a corpus of scientific publications. We evaluate the MFMO by asking questions that test the ability of the ontology to return appropriate answers (competency questions). We compare the results of queries of the MFMO to results from similar searches in PubMed and Google Scholar. Results and Significance: Our tests demonstrate that the MFMO is competent to answer queries formed in the common language of comparative anatomy, but PubMed and Google Scholar are not. Overall, our results show that by incorporating anatomical ontologies into searches, an expanded and anatomically comprehensive set of results

can be obtained. The broader scientific and publishing communities should consider taking up the challenge of semantically enabled search capabilities.

D'Souza, S. L., Holub, J. L., Pavic, B. T., & Rodriguez, S. A. (2016). A multicenter evaluation of the utilization of endoscopic ultrasound. *Digestive Endoscopy : Official Journal of the Japan Gastroenterological Endoscopy Society*,

OBJECTIVES: There are currently no data regarding the number and type of EUS procedures being performed in the United States. The aims of the study are to: 1) estimate the annual number of EUS procedures being performed in a nationwide database, 2) describe the indications and type of EUS performed, and 3) examine short-term trends in volume. METHODS:

Retrospective analysis from the Clinical Outcomes Research Initiative (CORI) of EUS procedures performed on patients > 18 years of age from January 1, 2010 through December 31, 2013.

RESULTS: 7,614 EUS cases were performed by 68 endoscopists at 18 sites over the study period, representing 1.7% of the total number of endoscopic procedures. The most common indications were evaluation of a pancreatic mass (14.7%), diagnostic sampling with fine needle aspiration (14.1%), and evaluation of a pancreatic cyst (14.0%). The number of EUS examinations and cases undergoing same day ERCP increased over the study period ($p < 0.0001$). Use of general anesthesia or deep sedation increased markedly from 37.8% to 82.8% of procedures ($p < 0.0001$). CONCLUSIONS: This is the largest survey of EUS practice in the United States.

Evaluation of the pancreas accounts for roughly 40% of the indications for EUS. Use of EUS increased over the study period, and the proportion performed with deep sedation or general anesthesia increased as well. These data may have implications regarding number of endosonographers who should be trained, as well as cost issues pertaining to increasing use of anesthesia providers and same-day ERCP.

Dugan, J., Griffiths, E., Snow, P., Rosenzweig, H., Lee, E., Brown, B., et al. (2015). Blau syndrome-associated Nod2 mutation alters expression of full-length NOD2 and limits responses to muramyl dipeptide in knock-in mice. *Journal of Immunology (Baltimore, Md.: 1950)*, 194(1), 349-357. The biochemical mechanism by which mutations in nucleotide-binding oligomerization domain containing 2 (NOD2) cause Blau syndrome is unknown. Several studies have examined the effect

of mutations associated with Blau syndrome in vitro, but none has looked at the implication of the mutations in vivo. To test the hypothesis that mutated NOD2 causes alterations in signaling pathways downstream of NOD2, we created a Nod2 knock-in mouse carrying the most common mutation seen in Blau syndrome, R314Q (corresponding to R334Q in humans). The endogenous regulatory elements of mouse Nod2 were unaltered. R314Q mice showed reduced cytokine production in response to i.p. and intravitreal muramyl dipeptide (MDP). Macrophages from R314Q mice showed reduced NF-kappaB and IL-6 responses, blunted phosphorylation of MAPKs, and deficient ubiquitination of receptor-interacting protein 2 in response to MDP. R314Q mice expressed a truncated 80-kDa form of NOD2 that was most likely generated by a posttranslational event because there was no evidence for a stop codon or alternative splicing event. Human macrophages from two patients with Blau syndrome also showed a reduction of both cytokine production and phosphorylation of p38 in response to MDP, indicating that both R314Q mice and cells from patients with Blau syndrome show reduced responses to MDP. These data indicate that the R314Q mutation when studied with the Nod2 endogenous regulatory elements left intact is associated with marked structural and biochemical changes that are significantly different from those observed from studies of the mutation using overexpression, transient transfection systems.

Dugi, D.D., III, Simhan, J., & Morey, A. F. (2016). Urethroplasty for stricture disease: Contemporary techniques and outcomes. *Urology*, 89, 12-18.

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

Dunn, K., Bayer, L. L., & Mody, S. K. (2016). Postpartum contraception: An exploratory study of lactation consultants' knowledge and practices. *Contraception*,

OBJECTIVE: Lactation consultants interact with women during the postpartum period; however, they may not have comprehensive education on postpartum contraception and the impact on breastfeeding. The aims of this study were to assess lactation consultants' knowledge and practices about postpartum contraception and assess whether lactation consultants are interested in more education on postpartum contraception. STUDY DESIGN: We distributed a 30-question survey to self-identified lactation consultants and recruited participants via email, social media and at the 2015 California Breastfeeding Summit. RESULTS: We surveyed a total of 194 lactation consultants. Seventy-seven percent (137/177) stated they offer advice about postpartum contraception and its impact on breastfeeding. The majority of lactation consultants felt the theoretical or proven risks outweighed the benefits or there was an unacceptable health risk for the progestin-only pill 76.3% (100/131), progestin injection 90.1% (118/131) and progestin implant 93.1% (122/131) if used within 21 days of delivery. Although 68.7% (92/134) reported prior education on postpartum contraception, 82.1% (110/134) reported wanting more education on this topic, specifically in the form of a webinar 61.9% (83/134). Only 29.9% (40/134) reported knowledge of the United States Centers for Disease Control and Prevention 2011 Medical Eligibility Criteria for Contraceptive Use (USMEC) guidance for postpartum contraception.

CONCLUSION: There is a disconnect between the USMEC guidance and lactation consultants' knowledge regarding the safety of immediate postpartum contraception. IMPLICATIONS: This study explores lactation consultants' knowledge and practices about postpartum contraception, demonstrating that more evidence-based education is needed on this topic.

Durrani, K., Kempen, J. H., Ying, G. S., Kacmaz, R. O., Artornsombudh, P., Rosenbaum, J. T., et al. (2016). Adalimumab for ocular inflammation. *Ocular Immunology and Inflammation*, , 1-8.

PURPOSE: To evaluate adalimumab as an immunomodulatory treatment for non-infectious ocular inflammatory diseases. METHODS: Characteristics of patients treated with adalimumab were abstracted in a standardized chart review. Main outcomes measured were control of inflammation, corticosteroid-sparing effect, and visual acuity. RESULTS: In total, 32 patients with ocular inflammation were treated with adalimumab. The most common ophthalmic diagnoses

were anterior uveitis, occurring in 15 patients (47%), and scleritis, occurring in 9 patients (28%). At 6 months of therapy, among 15 eyes with active inflammation, 7 (47%) became completely inactive, and oral prednisone was reduced to ≤ 10 mg/day in 2 of 4 patients (50%). On average, visual acuity decreased by 0.13 lines during the first 6 months of treatment. Adalimumab was discontinued because of lack of effectiveness in four patients within 6 months. CONCLUSIONS: Adalimumab was moderately effective in controlling inflammation in a group of highly pre-treated cases of ocular inflammatory disease.

Dwarkasing, J. T., Marks, D. L., Witkamp, R. F., & Van Norren, K. (2016). Hypothalamic inflammation and food intake regulation during chronic illness. *Peptides*, *77*, 60-66.

Anorexia is a common symptom in chronic illness. It contributes to malnutrition and strongly affects survival and quality of life. A common denominator of many chronic diseases is an elevated inflammatory status, which is considered to play a pivotal role in the failure of food-intake regulating systems in the hypothalamus. In this review, we summarize findings on the role of hypothalamic inflammation on food intake regulation involving hypothalamic neuropeptide Y (NPY) and pro-opiomelanocortin (POMC). Furthermore, we outline the role of serotonin in the inability of these peptide based food-intake regulating systems to respond and adapt to changes in energy metabolism during chronic disease. © 2015 Elsevier Inc. All rights reserved.

Ebrahim, S., Avenarius, M. R., Grati, M., Krey, J. F., Windsor, A. M., Sousa, A. D., et al. (2016).

Stereocilia-staircase spacing is influenced by myosin III motors and their cargos espin-1 and espin-like. *Nature Communications*, *7*, 10833.

Hair cells tightly control the dimensions of their stereocilia, which are actin-rich protrusions with graded heights that mediate mechanotransduction in the inner ear. Two members of the myosin-III family, MYO3A and MYO3B, are thought to regulate stereocilia length by transporting cargos that control actin polymerization at stereocilia tips. We show that eliminating espin-1 (ESPN-1), an isoform of ESPN and a myosin-III cargo, dramatically alters the slope of the stereocilia staircase in a subset of hair cells. Furthermore, we show that espin-like (ESPNL), primarily present in developing stereocilia, is also a myosin-III cargo and is essential for normal hearing. ESPN-1 and ESPNL each bind MYO3A and MYO3B, but differentially influence how the two motors

function. Consequently, functional properties of different motor-cargo combinations differentially affect molecular transport and the length of actin protrusions. This mechanism is used by hair cells to establish the required range of stereocilia lengths within a single cell.

Edelman, A. B., Cherala, G., Blue, S. W., Erikson, D. W., & Jensen, J. T. (2016). Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: Single and double dosing. *Contraception*,

OBJECTIVE: To determine if differences exist in the pharmacokinetics (PK) of levonorgestrel-based emergency contraception (LNG-EC) in obese and normal body mass index (BMI) users and test whether doubling the dose of LNG-EC in obese women increases total and free (active) LNG serum concentrations. STUDY DESIGN: Healthy, reproductive-age women with obese and normal BMIs received 1.5 mg LNG orally (ECx1) and then in a subsequent menstrual cycle, the obese group also received 3mg LNG (ECx2). Dosing occurred during the follicular phase. Total and free LNG PK parameters were obtained via serum samples through an indwelling catheter at 0, 0.5, 1, 1.5, 2, and 2.5 hours. The primary outcome was the difference in total and free LNG concentration maximum (C_{max}) between ECx1 and ECx2 in the obese group. RESULTS: A total of 10 women enrolled and completed the study (normal BMI = 5, median 22.8 kg/m², range 20.8-23.7; obese BMI = 5, 39.5 kg/m², range 35.9-46.7). The total LNG C_{max} for obese subjects following ECx1 (5.57±2.48 ng/mL) was significantly lower than the level observed in normal BMI women (10.30±2.47, p=0.027). Notably, ECx2 increased the C_{max} significantly (10.52±2.76, p=0.002); approximating the level in normal BMI subjects receiving ECx1. Free LNG C_{max} followed a similar pattern. CONCLUSION: Obesity adversely impacts both the total and free C_{max} levels of LNG EC and this likely explains its lack of efficacy in obese women. Doubling the dose appears to correct the obesity-related PK changes but additional research is needed to determine if this also improves EC effectiveness in obese women. IMPLICATIONS: This study demonstrates that obesity interferes with the pharmacokinetics of LNG EC, and that doubling the dose may be an effective strategy to improve its efficacy in obese women.

Eden, K. B., Totten, A. M., Kassakian, S. Z., Gorman, P. N., McDonagh, M. S., Devine, B., et al. (2016). Barriers and facilitators to exchanging health information: A systematic review.

International Journal of Medical Informatics, 88, 44-51.

Objectives: We conducted a systematic review of studies assessing facilitators and barriers to use of health information exchange (HIE). Methods: We searched MEDLINE, PsycINFO, CINAHL, and the Cochrane Library databases between January 1990 and February 2015 using terms related to HIE. English-language studies that identified barriers and facilitators of actual HIE were included. Data on study design, risk of bias, setting, geographic location, characteristics of the HIE, perceived barriers and facilitators to use were extracted and confirmed. Results: Ten cross-sectional, seven multiple-site case studies, and two before-after studies that included data from several sources (surveys, interviews, focus groups, and observations of users) evaluated perceived barriers and facilitators to HIE use. The most commonly cited barriers to HIE use were incomplete information, inefficient workflow, and reports that the exchanged information that did not meet the needs of users. The review identified several facilitators to use. Discussion: Incomplete patient information was consistently mentioned in the studies conducted in the US but not mentioned in the few studies conducted outside of the US that take a collective approach toward healthcare. Individual patients and practices in the US may exercise the right to participate (or not) in HIE which effects the completeness of patient information available to be exchanged. Workflow structure and user roles are key but understudied. Conclusions: We identified several facilitators in the studies that showed promise in promoting electronic health data exchange: obtaining more complete patient information; thoughtful workflow that folds in HIE; and inclusion of users early in implementation. © 2016 Elsevier Ireland Ltd.

El Rassi, E., Mace, J. C., Steele, T. O., Alt, J. A., Soler, Z. M., Fu, R., et al. (2016). Sensitivity analysis and diagnostic accuracy of the brief smell identification test in patients with chronic rhinosinusitis. *International Forum of Allergy and Rhinology, 6(3), 287-292.*

Background: The Brief Smell Identification Test (BSIT) is an abbreviated version of the Smell Identification Test (SIT) used to assess olfactory function. Although the BSIT can be efficiently administered in under 5 minutes, the accuracy of the BSIT in relation to the SIT in patients with chronic rhinosinusitis (CRS) is unknown. Methods: Patients with CRS were recruited as part of an ongoing multi-institutional observational cohort study. A total of 183 participants provided both BSIT and SIT olfactory function scores during initial enrollment. Linear associations between BSIT

and SIT scores were evaluated using Pearson's correlation coefficients (r_p). The sensitivity, specificity, and accuracy of BSIT scores were determined using SIT scores as the "gold standard." Results: A strong bivariate linear association was found between BSIT and SIT scores ($r_p = 0.893$; $p < 0.001$) for all participants. A significantly lower proportion of patients were identified as having abnormal olfaction using the BSIT compared to the SIT (47% vs 68%, respectively; $p < 0.001$). Using the currently defined score of $\hat{\alpha}\% \times 8$ as a cut-point for abnormal olfactory function, the BSIT demonstrated a sensitivity of 63% and specificity of 88% with an overall accuracy of 71%. Increasing the cut-point to $\hat{\alpha}\% \times 9$ resulted in an increased sensitivity of 86%, a specificity of 76%, and an improved overall accuracy of 83%. Conclusion: In patients with CRS, BSIT scores strongly correlate with SIT scores; however, the BSIT underestimates olfactory dysfunction as defined by the suggested cut-point of $\hat{\alpha}\% \times 8$. Increasing the cut-point to $\hat{\alpha}\% \times 9$ increased the sensitivity and accuracy of the BSIT. © 2016 ARS-AAOA, LLC.

Ellen Kreipke, R., Wang, Y., Miklas, J. W., Mathieu, J., & Ruohola-Baker, H. (2016). Metabolic remodeling in early development and cardiomyocyte maturation. *Seminars in Cell and Developmental Biology*, 52, 84-92.

Aberrations in metabolism contribute to a large number of diseases, such as diabetes, obesity, cancer, and cardiovascular diseases, that have a substantial impact on the mortality rates and quality of life worldwide. However, the mechanisms leading to these changes in metabolic state - and whether they are conserved between diseases - is not well understood. Changes in metabolism similar to those seen in pathological conditions are observed during normal development in a number of different cell types. This provides hope that understanding the mechanism of these metabolic switches in normal development may provide useful insight in correcting them in pathological cases. Here, we focus on the metabolic remodeling observed both in early stage embryonic stem cells and during the maturation of cardiomyocytes. © 2016 Elsevier Ltd.

Elliott, D. A., Nabavizadeh, N., Romer, J. L., Chen, Y., & Holland, J. M. (2016). Medical marijuana use in head and neck squamous cell carcinoma patients treated with radiotherapy. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*,

PURPOSE: The purpose of the study was to better understand why patients with history of head and neck cancer (HNC) treated with radiotherapy are using medical marijuana (MM). METHODS: Established HNC quality of life questionnaires and our own MM quality of life questionnaire were sent to 15 HNC patients treated at our institution who reported using MM. Patients are clinically disease free and currently using MM to manage long-term side effects after curative HNC treatment. RESULTS: There was a 100 % response rate. Median time from treatment was 45 months (21-136 months). Most patients smoked marijuana (12 patients), while others reported ingestion (4 patients), vaporizing (3 patients), and use of homemade concentrated oil (1 patient). Six patients reported prior recreational marijuana use before diagnosis. MM provided benefit in altered sense, weight maintenance, depression, pain, appetite, dysphagia, xerostomia, muscle spasm, and sticky saliva. CONCLUSIONS: HNC patients report MM use to help with long-term side effects of radiotherapy.

Ellis, C., Hoffman, W., Jaehnert, S., Plagge, J., Loftis, J. M., Schwartz, D., et al. (2016). Everyday problems with executive dysfunction and impulsivity in adults recovering from methamphetamine addiction. *Addictive Disorders and their Treatment*, 15(1), 1-5.

Objectives: Compared with nonaddicted controls (CTLs), adults in remission from methamphetamine addiction (MAREM) evidence impairments on objective measures of executive functioning and impulsivity. Methods: To evaluate the impact of these impairments in MA-REM adults, demographically matched groups (MA-REM, n=30; CTLs, n=24) completed objective and self-report measures of executive functioning and impulsivity. Results: MA-REM adults demonstrated significantly ($P < 0.050$) greater objective and subjective problems with executive functioning and impulsivity. Conclusions: These results suggest that adults in MA-REM are aware of their deficits and that these deficits have significant impact in everyday life. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Esbona, K., Inman, D., Saha, S., Jeffery, J., Schedin, P., Wilke, L., et al. (2016). COX-2 modulates mammary tumor progression in response to collagen density. *Breast Cancer Research : BCR*, 18(1), 35-016-0695-3.

BACKGROUND: High breast density is linked to an increased risk of breast cancer, and correlates

with changes in collagen. In a mouse model of mammary carcinoma in the context of increased collagen deposition, the MMTV-PyMT/Col1a1 (tm1jae) , there is accelerated mammary tumor formation and progression. Previous gene expression analysis suggests that increased collagen density elevates expression of PTGS2 (prostaglandin-endoperoxide synthase 2), the gene for cyclooxygenase-2 (COX-2). METHODS: To understand the role of COX-2 in tumor progression within a collagen-dense microenvironment, we treated MMTV-PyMT or MMTV-PyMT/Col1a1 (tm1jae) tumors prior to and after tumor formation. Animals received treatment with celecoxib, a specific COX-2 inhibitor, or placebo. Mammary tumors were examined for COX-2, inflammatory and stromal cell components, and collagen deposition through immunohistochemical analysis, immunofluorescence, multiplex cytokine ELISA and tissue imaging techniques. RESULTS: PyMT/Col1a1 (tm1jae) tumors were larger, more proliferative, and expressed higher levels of COX-2 and PGE2 than PyMT tumors in wild type (WT) mice. Treatment with celecoxib significantly decreased the induced tumor size and metastasis of the PyMT/Col1a1 tumors, such that their size was not different from the smaller PyMT tumors. Celecoxib had minimal effect on the PyMT tumors. Celecoxib decreased expression levels of COX-2, PGE2, and Ki-67. Several cytokines were over-expressed in PyMT/Col1a1 compared to PyMT, and celecoxib treatment prevented their over-expression. Furthermore, macrophage and neutrophil recruitment were enhanced in PyMT/Col1a1 tumors, and this effect was inhibited by celecoxib. Notably, COX-2 inhibition reduced overall collagen deposition. Finally, when celecoxib was used prior to tumor formation, PyMT/Col1a1 tumors were fewer and smaller than in untreated animals. CONCLUSION: These findings suggest that COX-2 has a direct role in modulating tumor progression in tumors arising within collagen-dense microenvironments, and suggest that COX-2 may be an effective therapeutic target for women with dense breast tissue and early-stage breast cancer.

Evans, C. P., Higano, C. S., Keane, T., Andriole, G., Saad, F., Iversen, P., et al. (2016). The PREVAIL study: Primary outcomes by site and extent of baseline disease for enzalutamide-treated men with chemotherapy-naive metastatic castration-resistant prostate cancer. *European Urology*,
BACKGROUND: Enzalutamide, an oral androgen receptor inhibitor, significantly improved overall survival (OS) and radiographic progression-free survival (rPFS) versus placebo in the PREVAIL trial of men with chemotherapy-naive metastatic castration-resistant prostate cancer.

OBJECTIVE: To assess the effects of enzalutamide versus placebo in patients from PREVAIL based on site and extent of baseline disease. DESIGN, SETTING, AND PARTICIPANTS: One thousand seven hundred and seventeen asymptomatic or minimally symptomatic patients were randomized to enzalutamide (n=872) or placebo (n=845). Subgroup analyses included nonvisceral (only bone and/or nodal; n=1513), visceral (lung and/or liver; n=204), low-volume bone disease (\geq 4 bone metastases; n=850), lymph node only disease (n=195). INTERVENTION: Oral enzalutamide (160mg) or placebo once daily while continuing androgen deprivation therapy. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Coprimary endpoints (rPFS, OS) were prospectively evaluated in nonvisceral and visceral subgroups. All other efficacy analyses were post hoc. RESULTS AND LIMITATIONS: Enzalutamide improved rPFS versus placebo in patients with nonvisceral disease (hazard ratio [HR], 0.18; 95% confidence interval [CI], 0.14-0.22), visceral disease (HR, 0.28; 95% CI, 0.16-0.49), low- or high-volume bone disease (HR, 0.16; 95% CI, 0.11-0.22; HR, 0.22; 95% CI, 0.16-0.29, respectively), and lymph node only disease (HR, 0.09; 95% CI, 0.04-0.19). For OS, HRs favored enzalutamide (1 in patients with visceral disease (HR, 0.82; 95% CI, 0.55-1.23). Enzalutamide was well tolerated in patients with or without visceral disease. CONCLUSIONS: Enzalutamide provided clinically significant benefits in men with chemotherapy-naïve metastatic castration-resistant prostate cancer, with or without visceral disease, low- or high-volume bone disease, or lymph node only disease. PATIENT SUMMARY: Patients with metastatic castration-resistant prostate cancer-including those with or without visceral disease or widespread bone disease-benefitted from enzalutamide, an active well-tolerated therapy.

Fan, D., Bradley, M. J., Hinkle, A. W., Johnson, R. L., & Tratnyek, P. G. (2016). Chemical reactivity probes for assessing abiotic natural attenuation by reducing iron minerals. *Environmental Science and Technology*, 50(4), 1868-1876.

Increasing recognition that abiotic natural attenuation (NA) of chlorinated solvents can be important has created demand for improved methods to characterize the redox properties of the aquifer materials that are responsible for abiotic NA. This study explores one promising approach: using chemical reactivity probes (CRPs) to characterize the thermodynamic and kinetic aspects of contaminant reduction by reducing iron minerals. Assays of thermodynamic CRPs were developed

to determine the reduction potentials (ECRP) of suspended minerals by spectrophotometric determination of equilibrium CRP speciation and calculations using the Nernst equation. ECRP varied as expected with mineral type, mineral loading, and Fe(II) concentration. Comparison of ECRP with reduction potentials measured potentiometrically using a Pt electrode (EPt) showed that ECRP was 100-150 mV more negative than EPt. When EPt was measured with small additions of CRPs, the systematic difference between EPt and ECRP was eliminated, suggesting that these CRPs are effective mediators of electron transfer between mineral and electrode surfaces. Model contaminants (4-chloronitrobenzene, 2-chloroacetophenone, and carbon tetrachloride) were used as kinetic CRPs. The reduction rate constants of kinetic CRPs correlated well with the ECRP for mineral suspensions. Using the rate constants compiled from literature for contaminants and relative mineral reduction potentials based on ECRP measurements, qualitatively consistent trends were obtained, suggesting that CRP-based assays may be useful for estimating abiotic NA rates of contaminants in groundwater. © 2016 American Chemical Society.

Farsad, K., & Kaufman, J. A. (2016). Novel image guidance techniques for portal vein targeting during transjugular intrahepatic portosystemic shunt creation. *Techniques in Vascular and Interventional Radiology*, 19(1), 10-20.

The most challenging part of transjugular intrahepatic portosystemic shunt creation is arguably the transvenous access from the hepatic vein to the portal vein. As experience and technology have evolved, the image guidance aspect of this critical step in the procedure has become more robust. Improved means to target the portal vein include both direct and indirect methods of portal vein opacification, cross-sectional imaging for both targeting and access, and novel use of transabdominal and intravascular ultrasound guidance. These techniques are described herein.

Feng, Z., Jensen, S. M., Messenheimer, D. J., Farhad, M., Neuberger, M., Bifulco, C. B., et al. (2016). Multispectral imaging of T and B cells in murine spleen and tumor. *Journal of Immunology (Baltimore, Md.: 1950)*,

Recent advances in multiplex immunohistochemistry techniques allow for quantitative, spatial identification of multiple immune parameters for enhanced diagnostic and prognostic insight.

However, applying such techniques to murine fixed tissues, particularly sensitive epitopes, such as CD4, CD8alpha, and CD19, has been difficult. We compared different fixation protocols and Ag-retrieval techniques and validated the use of multiplex immunohistochemistry for detection of CD3+CD4+ and CD3+CD8+ T cell subsets in murine spleen and tumor. This allows for enumeration of these T cell subsets within immune environments, as well as the study of their spatial distribution.

Fenske, T. S., Ahn, K. W., Graff, T. M., DiGilio, A., Bashir, Q., Kamble, R. T., et al. (2016). Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. *British Journal of Haematology*,
For diffuse large B-cell lymphoma (DLBCL) patients progressing after autologous haematopoietic cell transplantation (autoHCT), allogeneic HCT (alloHCT) is often considered, although limited information is available to guide patient selection. Using the Center for International Blood and Marrow Transplant Research (CIBMTR) database, we identified 503 patients who underwent alloHCT after disease progression/relapse following a prior autoHCT. The 3-year probabilities of non-relapse mortality, progression/relapse, progression-free survival (PFS) and overall survival (OS) were 30, 38, 31 and 37% respectively. Factors associated with inferior PFS on multivariate analysis included Karnofsky performance status (KPS) <80, chemoresistance, autoHCT to alloHCT interval <1-year and myeloablative conditioning. Factors associated with worse OS on multivariate analysis included KPS<80, chemoresistance and myeloablative conditioning. Three adverse prognostic factors were used to construct a prognostic model for PFS, including KPS<80 (4 points), autoHCT to alloHCT interval <1-year (2 points) and chemoresistant disease at alloHCT (5 points). This CIBMTR prognostic model classified patients into four groups: low-risk (0 points), intermediate-risk (25 points), high-risk (69 points) or very high-risk (11points), predicting 3-year PFS of 40, 32, 11 and 6%, respectively, with 3-year OS probabilities of 43, 39, 19 and 11% respectively. In conclusion, the CIBMTR prognostic model identifies a subgroup of DLBCL patients experiencing long-term survival with alloHCT after a failed prior autoHCT.

Fernando, S. J., Leitenberger, S., Majerus, M., Krol, A., & MacArthur, C. J. (2016). Use of intravenous propranolol for control of a large cervicofacial hemangioma in a critically ill neonate. *International*

Journal of Pediatric Otorhinolaryngology, 84, 52-54.

Cervicofacial segmental infantile hemangiomas (IH) may result in airway obstruction requiring use of propranolol to induce hemangioma regression and reestablish the airway. We present the first case using intravenous (IV) propranolol for control of airway obstruction and rapid expansion of cervicofacial IH in the setting of necrotizing enterocolitis (NEC) impaired gastrointestinal function. Intravenous dosing of propranolol was tolerated well in a critically ill neonate with multisystem complications of prematurity. © 2016 Elsevier Ireland Ltd.

Fischer, J. M., Dudley, S., Miller, A. J., & Liskay, R. M. (2016). An intact Pms2 ATPase domain is not essential for male fertility. *DNA Repair*, 39, 46-51.

The DNA mismatch repair (MMR) machinery in mammals plays critical roles in both mutation avoidance and spermatogenesis. Meiotic analysis of knockout mice of two different MMR genes, Mlh1 and Mlh3, revealed both male and female infertility associated with a defect in meiotic crossing over. In contrast, another MMR gene knockout, Pms2 (Pms2ko/ko), which contained a deletion of a portion of the ATPase domain, produced animals that were male sterile but female fertile. However, the meiotic phenotype of Pms2ko/ko males was less clear-cut than for Mlh1- or Mlh3-deficient meiosis. More recently, we generated a different Pms2 mutant allele (Pms2cre), which results in deletion of the same portion of the ATPase domain. Surprisingly, Pms2cre/cre male mice were completely fertile, suggesting that the ATPase domain of Pms2 is not required for male fertility. To explore the difference in male fertility, we examined the Pms2 RNA and found that alternative splicing of the Pms2cre allele results in a predicted Pms2 containing the C-terminus, which contains the Mlh1-interaction domain, a possible candidate for stabilizing Mlh1 levels. To study further the basis of male fertility, we examined Mlh1 levels in testes and found that whereas Pms2 loss in Pms2ko/ko mice results in severely reduced levels of Mlh1 expression in the testes, Mlh1 levels in Pms2cre/cre testes were reduced to a lesser extent. Thus, we propose that a primary function of Pms2 during spermatogenesis is to stabilize Mlh1 levels prior to its critical crossing over function with Mlh3. © 2015 Elsevier B.V.

Flickinger, T. E., Saha, S., Roter, D., Korthuis, P., Sharp, V., Cohn, J., et al. (2016). Clinician empathy is associated with differences in patient-clinician communication behaviors and higher medication

self-efficacy in HIV care. *Patient Education and Counseling*, 99(2), 220-226.

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. © 2015 Elsevier Ireland Ltd.

Flickinger, T. E., Saha, S., Roter, D., Korhuis, P. T., Sharp, V., Cohn, J., et al. (2016). Respecting patients is associated with more patient-centered communication behaviors in clinical encounters. *Patient Education and Counseling*, 99(2), 250-255.

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. © 2015 Elsevier Ireland Ltd.

Folmes, C. D., Ma, H., Mitalipov, S., & Terzic, A. (2016). Mitochondria in pluripotent stem cells: Stemness regulators and disease targets. *Current Opinion in Genetics & Development, 38*, 1-7. Beyond their canonical role in efficient ATP production through oxidative metabolism, mitochondria are increasingly recognized as critical in defining stem cell function and fate. Implicating a fundamental interplay within the epigenetics of eukaryotic cell systems, the integrity of mitochondria is found vital across the developmental/differentiation spectrum from securing pluripotency maintenance to informing organotypic decisions. This overview will discuss recent progress on examining the plasticity of mitochondria in enabling the execution of programming and reprogramming regimens, as well as the application of nuclear reprogramming and somatic cell nuclear transfer as rescue techniques to generate genetically and functionally corrected pluripotent stem cells from patients with mitochondrial DNA-based disease.

Fowler, J. R., Eggleston, J. L., Reavis, K. M., McMillan, G. P., & Reiss, L. A. J. (2016). Effects of removing low-frequency electric information on speech perception with bimodal hearing. *Journal of Speech, Language, and Hearing Research, 59*(1), 99-109.

Purpose: The objective was to determine whether speech perception could be improved for bimodal listeners (those using a cochlear implant [CI] in one ear and hearing aid in the contralateral ear) by removing low-frequency information provided by the CI, thereby reducing acoustic-electric overlap. Method: Subjects were adult CI subjects with at least 1 year of CI

experience. Nine subjects were evaluated in the CI-only condition (control condition), and 26 subjects were evaluated in the bimodal condition. CIs were programmed with 4 experimental programs in which the low cutoff frequency (LCF) was progressively raised. Speech perception was evaluated using Consonant-Nucleus-Consonant words in quiet, AzBio sentences in background babble, and spondee words in background babble. Results: The CI-only group showed decreased speech perception in both quiet and noise as the LCF was raised. Bimodal subjects with better hearing in the hearing aid ear (60 dB HL at 250 and 500 Hz) performed similarly to the CI-only group. Conclusions: These findings suggest that reducing low-frequency overlap of the CI and contralateral hearing aid may improve performance in quiet for some bimodal listeners with better hearing. © 2016 American Speech-Language-Hearing Association.

Freeman, M. D., & Zeegers, M. (2015). Principles and applications of forensic epidemiology in the medicolegal setting. *Law, Probability and Risk, 14*(4), 269-278.

The discipline of forensic epidemiology, a branch of forensic medicine, provides a systematic approach to the assessment of general and specific (individual) causation, with the results suitable for presentation in a court of law. In the present paper some of the methods utilized in forensic epidemiology are described, along with examples of how such methods can be reliably applied to the evaluation of specific causality in criminal and civil matters. Included in the discussion is the presentation of two case studies in applied forensic epidemiology; one in a civil action for medical negligence, and the other in a homicide investigation. © The Author [2015]. Published by Oxford University Press.

Freiman, M. R., Clark, J. A., Slatore, C. G., Gould, M. K., Woloshin, S., Schwartz, L. M., et al. (2016).

Patients' knowledge, beliefs, and distress associated with detection and evaluation of incidental pulmonary nodules for cancer: Results from a multicenter survey. *Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer*,

INTRODUCTION: Pulmonary nodules are detected in more than 1 million Americans each year.

Prior qualitative work suggests that the detection of incidental pulmonary nodules can be burdensome for patients, but whether these findings generalize to a broader sample of patients is unknown. We categorized patients' knowledge, beliefs, and distress associated with detection and

evaluation of a pulmonary nodule, as well as their impressions of clinician communication.

METHODS: We administered a cross-sectional survey to adults with an incidental pulmonary nodule who were recruited from a rural medical center, an urban safety net hospital, and a Veterans Affairs hospital. **RESULTS:** Of the 490 individuals mailed surveys, 244 (50%) responded. Median nodule size was 7 mm, mean patient age was 67 years, 29% of respondents were female, and 86% were white. A quarter of the respondents (26%) reported clinically significant distress related to their nodule, our primary outcome, as measured by the Impact of Event Scale. Patients reported multiple concerns, including uncertainty about the nodule's cause (78%), the possibility of cancer (73%), and the possible need for surgery (64%). Only 25% of patients accurately estimated their lung cancer risk (within 15% of their actual risk); overall, there was no correlation between perceived and actual risk ($r = -0.007$, $p = 0.93$). The 23% of patients who did receive information on cancer risk from their provider were more likely to find this information reassuring (16%) than scary (7%). **CONCLUSION:** A quarter of patients with incidental pulmonary nodules experienced clinically significant distress. Knowledge about cancer risk and evaluation was poor. Clinician communication may help bridge knowledge gaps and alleviate distress in some patients.

French, J. D., Johnatty, S. E., Lu, Y., Beesley, J., Gao, B., Kalimutho, M., et al. (2015). Germline polymorphisms in an enhancer of PSIP1 are associated with progression-free survival in epithelial ovarian cancer. *Oncotarget*, 7(6), 6353-6368.

Women with epithelial ovarian cancer (EOC) are usually treated with platinum/taxane therapy after cytoreductive surgery but there is considerable inter-individual variation in response. To identify germline single-nucleotide polymorphisms (SNPs) that contribute to variations in individual responses to chemotherapy, we carried out a multi-phase genome-wide association study (GWAS) in 1,244 women diagnosed with serous EOC who were treated with the same first-line chemotherapy, carboplatin and paclitaxel. We identified two SNPs (rs7874043 and rs72700653) in TTC39B (best $P=7 \times 10^{-5}$, HR=1.90, for rs7874043) associated with progression-free survival (PFS). Functional analyses show that both SNPs lie in a putative regulatory element (PRE) that physically interacts with the promoters of PSIP1, CCDC171 and an alternative promoter of TTC39B. The C allele of rs7874043 is associated with poor PFS and showed increased

binding of the Sp1 transcription factor, which is critical for chromatin interactions with PSIP1. Silencing of PSIP1 significantly impaired DNA damage-induced Rad51 nuclear foci and reduced cell viability in ovarian cancer lines. PSIP1 (PC4 and SFRS1 Interacting Protein 1) is known to protect cells from stress-induced apoptosis, and high expression is associated with poor PFS in EOC patients. We therefore suggest that the minor allele of rs7874043 confers poor PFS by increasing PSIP1 expression.

Friedman, A., Howard, J., Shaw, E. K., Cohen, D. J., Shahidi, L., & Ferrante, J. M. (2016). Facilitators and barriers to care coordination in patient-centered medical homes (PCMHs) from coordinators' perspectives. *Journal of the American Board of Family Medicine, 29*(1), 90-101.

Background: Care coordinators are increasingly featured in patient-centered medical home (PCMH) projects, yet little research examines how coordinators themselves define and experience their role. This is the first study describing experiences of care coordinators across the US from their own perspectives. Methods: This qualitative study used a 5-month private, online discussion forum to gather data from 25 care coordinators from PCMH practices representing diversity in practice size, setting, and type. Participants answered questions and interacted with one another, creating an online social learning collaborative while allowing for data collection for research. Results: Coordinators identified barriers and facilitators in their work at the organization/system level, the interpersonal level, and the individual level. Some factors emerged as both barriers and facilitators, including the functionality of clinical information technology; the availability of community resources; interactions with clinicians and other health care facilities; interactions with patients; and self-care practices for mental health and wellness. Colocation and full integration into practices were other key facilitators, whereas excessive case loads and data management responsibilities were felt to be important barriers. Conclusions: While all the barriers and facilitators were important to performing coordinators' roles, relationship building materialized as key to effective care coordination, whether with clinicians, patients, or outside organizations. We discuss implications for practice and provide suggestions for further research.

Friedman, A. N., & Wolfe, B. (2016). Is bariatric surgery an effective treatment for type II diabetic kidney disease? *Clinical Journal of the American Society of Nephrology, 11*(3), 528-535.

Type II diabetic kidney disease is devastating to patients and society alike. This review will evaluate bariatric surgery as a treatment for diabetic kidney disease primarily through its ability to induce and maintain regression of type II diabetes. The review begins by outlining the global challenge of diabetic kidney disease, its link to obesity, and the comparative benefits of bariatric surgery on weight and type II diabetes. It then surveys comprehensively the relevant literature, which reports that although bariatric surgery is associated with reductions in albuminuria, its effect on harder clinical end points like progression of diabetic kidney disease is not known. The review also includes a critical assessment of the risks and costs of bariatric surgery and concludes by acknowledging the major knowledge gaps in the field and providing research strategies to overcome them. Until these knowledge gaps are filled, clinicians will be forced to rely on their own subjective judgment in determining the benefit-risk ratio of bariatric surgery for patients with diabetic kidney disease. © 2016 by the American Society of Nephrology.

Friedman, M. A., & Winthrop, K. (2016). Vaccinations for rheumatoid arthritis. *Current Opinion in Rheumatology*,

PURPOSE OF REVIEW: Rheumatoid arthritis (RA) patients experience increased infectious disease-related morbidity and mortality, and vaccinations represent an important element in their care. However, vaccine immunogenicity can be affected by disease-modifying antirheumatic drug (DMARD) therapy, such that vaccine choice and timing can be clinically challenging. We review the indications, safety, and immunogenicity of vaccines in the setting of RA. RECENT FINDINGS: Recent recommendations highlight the use of influenza, pneumococcal, and shingles vaccines in RA patients. Studies suggest influenza and pneumococcal vaccines are underutilized, but well tolerated in RA patients and generally immunogenic during DMARD use with the exception of rituximab. Though data for other nonlive vaccines are more limited, hepatitis B virus and human papilloma virus vaccines also appear well tolerated and immunogenic in this population. Live vaccines for shingles and yellow fever remain contraindicated in some RA patients; however, limited data suggest they might be well tolerated in certain individuals. SUMMARY: The review updates rheumatologists on the optimal use and timing of routine vaccinations in the care of RA. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Frishman, G. N., Bell, C. L., Botros, S., Brost, B. C., Robinson, R. D., Steinauer, J., et al. (2016).

Applying to subspecialty fellowship: Clarifying the confusion and conflicts. *American Journal of Obstetrics and Gynecology*, 214(2), 243-246.

Of graduating obstetrics and gynecology residents, 40% apply for fellowship training and this percentage is likely to increase. The fellowship interview process creates a substantial financial burden on candidates as well as significant challenges in scheduling the multiple interviews for residents, residency programs, and fellowship programs. Coverage with relatively short lead time is needed for some resident rotations, multiple residents may request time off during overlapping time periods, and applicants may not be able to interview based on conflicting interview dates or the inability to find coverage from other residents for their clinical responsibilities. To address these issues, we propose that each subspecialty fellowship within obstetrics and gynecology be allocated a specified and limited time period to schedule their interviews with minimal overlap between subspecialties. Furthermore, programs in close geographic areas should attempt to coordinate their interview dates. This will allow residents to plan their residency rotation schedules far in advance to minimize the impact on rotations that are less amenable to time away from their associated clinical duties, and decrease the numbers of residents needing time off for interviews during any one time period. In addition, a series of formal discussions should take place between subspecialties related to these issues as well as within subspecialties to facilitate coordination. © 2016 Elsevier Inc.

Fromme, E. K., Holliday, E. B., Nail, L. M., Lyons, K. S., Hribar, M. R., & Thomas, C. R., Jr. (2016).

Computerized patient-reported symptom assessment in radiotherapy: A pilot randomized, controlled trial. *Supportive Care in Cancer*, 24(4), 1897-1906.

Purpose: Computer-based, patient-reported symptom survey tools have been described for patients undergoing chemotherapy. We hypothesized that patients undergoing radiotherapy might also benefit, so we developed a computer application to acquire symptom ratings from patients and generate summaries for use at point of care office visits and conducted a randomized, controlled pilot trial to test its feasibility. Methods: Subjects were randomized prior to beginning radiotherapy. Both control and intervention group subjects completed the computerized symptom assessment, but only for the intervention group were printed symptom

summaries made available before each weekly office visit. Metrics compared included the Global Distress Index (GDI), concordance of patient-reported symptoms and symptoms discussed by the physician and numbers of new and/or adjusted symptom management medications prescribed. Results: One hundred twelve patients completed the study: 54 in the control and 58 in the intervention arms. There were no differences in GDI over time between the control and intervention groups. In the intervention group, more patient-reported symptoms were actually discussed in radiotherapy office visits: 46/202 vs. 19/230. A sensitivity analysis to account for within-subjects correlation yielded 23.2 vs. 10.3 % ($p = 0.03$). Medications were started or adjusted at 15.4 % (43/280) of control visits compared to 20.4 % (65/319) of intervention visits ($p = 0.07$). Conclusions: This computer application is easy to use and makes extensive patient-reported outcome data available at the point of care. Although no differences were seen in symptom trajectory, patients who had printed symptom summaries had improved communication during office visits and a trend towards a more active symptom management during radiotherapy. © 2015, Springer-Verlag Berlin Heidelberg.

Fu, R., & Holmer, H. K. (2016). Change score or followup score? choice of mean difference estimates could impact meta-analysis conclusions. *Journal of Clinical Epidemiology*,

OBJECTIVE: In randomized controlled clinical trials, continuous outcomes are typically measured at both baseline and followup, and mean difference could be estimated using the change scores from baseline, or the followup scores. This study assesses the impact of using change score versus followup score on the conclusions of meta-analyses. STUDY DESIGN AND SETTING: A total of 63 meta-analyses from 6 comparative effectiveness reviews were included. The combined mean difference was estimated using a random effects model and we also evaluated whether the impact qualitatively varied by alternative random effects estimates. RESULTS: Based on the DerSimonian-Laird (DL) method, using the change versus the followup score led to 5 meta-analyses (7.9%) showing discrepancy in conclusions. Based on the profile likelihood (PL) method, 9 (14.3%) showed discrepancy in conclusions. Using change score was more likely to show a significant difference in effects between interventions (DL method: 4 out of 5; PL method: 7 out of 9). A significant difference in baseline scores did not necessarily lead to discrepancies in conclusions. CONCLUSIONS: Using the change versus the followup score could lead to important

discrepancies in conclusions. Sensitivity analyses should be conducted to check the robustness of results to the choice of mean difference estimates.

Fugolin, A. P. P., Correr-Sobrinho, L., Correr, A. B., Sinhoreti, M. A. C., Guiraldo, R. D., & Consani, S. (2016). Influence of irradiance on knoop hardness, degree of conversion, and polymerization shrinkage of nanofilled and microhybrid composite resins. *General Dentistry*, *64*(2), 26-31.

The purpose of this study was to investigate the influence of the irradiance emitted by a light-curing unit on microhardness, degree of conversion (DC), and gaps resulting from shrinkage of 2 dental composite resins. Cylinders of nanofilled and microhybrid composites were fabricated and light cured. After 24 hours, the tops and bottoms of the specimens were evaluated via indentation testing and Fourier transform infrared spectroscopy to determine Knoop hardness number (KHN) and DC, respectively. Gap width (representing polymerization shrinkage) was measured under a scanning electron microscope. The nanofilled composite specimens presented significantly greater KHNs than did the microhybrid specimens ($P < 0.05$). The microhybrid composite resin exhibited significantly greater DC and gap width than the nanofilled material ($P < 0.05$). Irradiance had a mostly material-dependent influence on the hardness and DC, but not the polymerization shrinkage, of composite resins.

Furuno, J. P., Noble, B. N., & Fromme, E. K. (2016). Should we refrain from antibiotic use in hospice patients? *Expert Review of Anti-Infective Therapy*, *14*(3), 277-280.

Gaddini, G. W., Turner, R. T., Grant, K. A., & Iwaniec, U. T. (2016). Alcohol: A simple nutrient with complex actions on bone in the adult skeleton. *Alcoholism: Clinical and Experimental Research*,

Background: Alcohol is an important nonessential component of diet, but the overall impact of drinking on bone health, especially at moderate levels, is not well understood. Bone health is important because fractures greatly reduce quality of life and are a major cause of morbidity and mortality in the elderly. Regular alcohol consumption is most common following skeletal maturity, emphasizing the importance of understanding the skeletal consequences of drinking in adults.

Methods: This review focuses on describing the complex effects of alcohol on the adult skeleton. Studies assessing the effects of alcohol on bone in adult humans as well as skeletally mature animal models published since the year 2000 are emphasized. Results: Light to moderate alcohol

consumption is generally reported to be beneficial, resulting in higher bone mineral density (BMD) and reduced age-related bone loss, whereas heavy alcohol consumption is generally associated with decreased BMD, impaired bone quality, and increased fracture risk. Bone remodeling is the principal mechanism for maintaining a healthy skeleton in adults and dysfunction in bone remodeling can lead to bone loss and/or decreased bone quality. Light to moderate alcohol may exert beneficial effects in older individuals by slowing the rate of bone remodeling, but the impact of light to moderate alcohol on bone remodeling in younger individuals is less certain. The specific effects of alcohol on bone remodeling in heavy drinkers are even less certain because the effects are often obscured by unhealthy lifestyle choices, alcohol-associated disease, and altered endocrine signaling. Conclusions: Although there have been advances in understanding the complex actions of alcohol on bone, much remains to be determined. Limited evidence implicates age, skeletal site evaluated, duration, and pattern of drinking as important variables. Few studies systematically evaluating the impact of these factors have been conducted and should be made a priority for future research. In addition, studies performed in skeletally mature animals have potential to reveal mechanistic insights into the precise actions of alcohol and associated comorbidity factors on bone remodeling. © 2016 Research Society on Alcoholism.

Ganzini, L., & Back, A. L. (2016). The challenge of new legislation on physician-assisted death. *JAMA Internal Medicine*,

Garbati, M. R., Hays, L. E., Keaney Rathbun, R., Jillette, N., Chin, K., Al-Dhalimy, M., et al. (2016). Cytokine overproduction and crosslinker hypersensitivity are unlinked in fanconi anemia macrophages. *Journal of Leukocyte Biology*, 99(3), 455-465.

The Fanconi anemia proteins participate in a canonical pathway that repairs cross-linking agent-induced DNA damage. Cells with inactivated Fanconi anemia genes are universally hypersensitive to such agents. Fanconi anemia-deficient hematopoietic stem cells are also hypersensitive to inflammatory cytokines, and, as importantly, Fanconi anemia macrophages overproduce such cytokines in response to TLR4 and TLR7/8 agonists. We questioned whether TLR-induced DNA damage is the primary cause of aberrantly regulated cytokine production in Fanconi anemia

macrophages by quantifying TLR agonist-induced TNF- $\hat{I}\pm$ production, DNA strand breaks, crosslinker-induced chromosomal breakage, and Fanconi anemia core complex function in Fanconi anemia complementation group C-deficient human and murine macrophages. Although both M1 and M2 polarized Fanconi anemia cells were predictably hypersensitive to mitomycin C, only M1 macrophages overproduced TNF- $\hat{I}\pm$ in response to TLR-activating signals. DNA damaging agents alone did not induce TNF- $\hat{I}\pm$ production in the absence of TLR agonists in wild-type or Fanconi anemia macrophages, and mitomycin C did not enhance TLR responses in either normal or Fanconi anemia cells. TLR4 and TLR7/8 activation induced cytokine overproduction in Fanconi anemia macrophages. Also, although TLR4 activation was associated with induced double strand breaks, TLR7/8 activation was not. That DNA strand breaks and chromosome breaks are neither necessary nor sufficient to account for the overproduction of inflammatory cytokines by Fanconi anemia cells suggests that noncanonical anti-inflammatory functions of Fanconi anemia complementation group C contribute to the aberrant macrophage phenotype and suggests that suppression of macrophage/TLR hyperreactivity might prevent cytokine-induced stem cell attrition in Fanconi anemia. Â© Society for Leukocyte Biology.

Garbati, M. R., Welgan, C. A., Landefeld, S. H., Newell, L. F., Agarwal, A., Dunlap, J. B., et al. (2016).

Mutant calreticulin-expressing cells induce monocyte hyperreactivity through a paracrine mechanism. *American Journal of Hematology*, 91(2), 211-219.

Mutations in the calreticulin gene (CALR) were recently identified in approximately 70-80% of patients with JAK2-V617F-negative essential thrombocytosis and primary myelofibrosis. All frameshift mutations generate a recurring novel C-terminus. Here we provide evidence that mutant calreticulin does not accumulate efficiently in cells and is abnormally enriched in the nucleus and extracellular space compared to wildtype calreticulin. The main determinant of these findings is the loss of the calcium-binding and KDEL domains. Expression of type I mutant CALR in Ba/F3 cells confers minimal IL-3-independent growth. Interestingly, expression of type I and type II mutant CALR in a nonhematopoietic cell line does not directly activate JAK/STAT signaling compared to wildtype CALR and JAK2-V617F expression. These results led us to investigate paracrine mechanisms of JAK/STAT activation. Here we show that conditioned media from cells expressing type I mutant CALR exaggerate cytokine production from normal monocytes with or

without treatment with a toll-like receptor agonist. These effects are not dependent on the novel C-terminus. These studies offer novel insights into the mechanism of JAK/STAT activation in patients with JAK2-V617F-negative essential thrombocytosis and primary myelofibrosis. © 2016 Wiley Periodicals, Inc.

Garon, E. B., Abarca, P. A., Strunck, J. L., Nameth, D., Neumann, C., Wolf, B., et al. (2015). Clinical trials in non-small cell lung cancer with biomarker-driven treatment allocation: Ready or not, here we come. *Critical Reviews in Oncogenesis*, 20(5-6), 339-348.

Lung cancer is the leading cause of cancer mortality. Great advances in non-small cell lung cancer therapy have been seen in the last decade, beginning with the success in treating lung cancer harboring EGFR mutations and ALK-gene rearrangements. The potential of these biomarker-driven therapies has propelled research in biomarker targeted approaches to the forefront of lung cancer research. The successful development of immunotherapeutic agents targeting PD-L1 and PD-1 with an associated non-genomic biomarker has opened a new front in the effort for targeted approaches. Although early-phase lung cancer studies have hinted at the potential to use biomarkers to select patients for allocation to treatment in the conduct of clinical trials, data from late-phase studies have tempered expectations. The data leave unclear the wisdom of routinely restricting enrollment on lung cancer clinical trials to biomarker restricted populations, particularly non-genomic biomarkers. © 2015 by Begell House, Inc.

Gera, G., McGlade, K. E., Reisman, D. S., & Scholz, J. P. (2016). Trunk muscle coordination during upward and downward reaching in stroke survivors. *Motor Control*, 20(1), 50-69.

In this study, we investigated deficits in coordination of trunk muscle modes involved in the stabilization of the trunk's trajectory for reaching upward and downward beyond functional arm length. Trunk muscle activity from 10 stroke survivors (8 men, 2 women; 64.1 +/- 10.5 years old) and 9 healthy control subjects (7 men, 2 women; 59.3 +/- 9.3 years old) was analyzed. Coordination of trunk muscle modes to stabilize the trunk trajectory was investigated using the uncontrolled manifold (UCM) analysis. The UCM analysis decomposes the variability of muscle modes into good and bad variability. The good variability does not affect the control of trunk motion, whereas the bad variability does. In stroke survivors, deficits in the ability to flexibly

combine trunk muscle modes was associated with reduced ability to minimize those combinations of trunk muscle modes that led to an error in trunk trajectory (bad variability), and this had a greater effect on reaching upward. This reduced coordination of trunk muscle modes during reaching was correlated with a clinical measure of trunk impairment.

Geron, C., Daly, R., Harley, P., Rasmussen, R., Seco, R., Guenther, A., et al. (2016). Large drought-induced variations in oak leaf volatile organic compound emissions during PINOT NOIR 2012. *Chemosphere*, 146, 8-21.

Leaf-level isoprene and monoterpene emissions were collected and analyzed from five of the most abundant oak (*Quercus*) species in Central Missouri's Ozarks Region in 2012 during PINOT NOIR (Particle Investigations at a Northern Ozarks Tower - NO_x, Oxidants, Isoprene Research). June measurements, prior to the onset of severe drought, showed isoprene emission rates and leaf temperature responses similar to those previously reported in the literature and used in Biogenic Volatile Organic Compound (BVOC) emission models. During the peak of the drought in August, isoprene emission rates were substantially reduced, and response to temperature was dramatically altered, especially for the species in the red oak subgenus (*Erythrobalanus*). *Quercus stellata* (in the white oak subgenus *Leucobalanus*), on the other hand, increased its isoprene emission rate during August, and showed no decline at high temperatures during June or August, consistent with its high tolerance to drought and adaptation to xeric sites at the prairie-deciduous forest interface. Mid-late October measurements were conducted after soil moisture recharge, but were affected by senescence and cooler temperatures. Isoprene emission rates were considerably lower from all species compared to June and August data. The large differences between the oaks in response to drought emphasizes the need to consider BVOC emissions at the species level instead of just the whole canopy. Monoterpene emissions from *Quercus rubra* in limited data were highest among the oaks studied, while monoterpene emissions from the other oak species were 80-95% lower and less than assumed in current BVOC emission models. Major monoterpenes from *Q. rubra* (and in ambient air) were p-cymene, α -pinene, β -pinene, d-limonene, γ -terpinene, β -ocimene (predominantly 1,3,7-trans- β -ocimene, but also 1,3,6-trans- β -ocimene), tricyclene, α -terpinene, sabinene, terpinolene, and myrcene. Results are discussed in the context of canopy flux studies conducted at the site during PINOT NOIR,

which are described elsewhere. The leaf isoprene emissions before and during the drought were consistent with above canopy fluxes, while leaf and branch monoterpene emissions were an order of magnitude lower than the observed above canopy fluxes, implying that other sources may be contributing substantially to monoterpene fluxes at this site. This strongly demonstrates the need for further simultaneous canopy and enclosure BVOC emission studies. © 2015 .

Gold, R., Esterberg, E., Hollombe, C., Arkind, J., Vakarcs, P. A., Tran, H., et al. (2016). Low back imaging when not indicated: A descriptive cross-system analysis. *The Permanente Journal*, 20(2), 10.7812/TPP/15-081.

CONTEXT: Guideline-discordant imaging to evaluate incident low back pain is common.

OBJECTIVE: We compared rates of guideline-discordant imaging in patients with low back pain in two care delivery systems with differing abilities to track care through an electronic health record (EHR), and in their patients' insurance status, to measure the association between these factors and rates of ordered low back imaging. DESIGN: We used data from two Kaiser Permanente (KP) Regions and from OCHIN, a community health center network. We extracted data on imaging performed after index visits for low back pain from June 1, 2011, to May 31, 2012, in these systems. Adjusted logistic regression measured associations between system-level factors and imaging rates. MAIN OUTCOME MEASURES: Imaging rates for incident low back pain using 2 national quality metrics: Clinical Quality Measure 0052, a measure for assessing Meaningful Use of EHRs, and the Healthcare Effectiveness Data and Information Set measure "Use of Imaging Studies for Low Back Pain." RESULTS: Among 19,503 KP patients and 2694 OCHIN patients with incident low back pain, ordered imaging was higher among men and whites but did not differ across health care systems. OCHIN's publicly insured patients had higher rates of imaging compared with those with private or no insurance. CONCLUSION: Rates of ordered imaging to evaluate incident low back pain among uninsured OCHIN patients were lower than in KP overall; among insured OCHIN patients, rates were higher than in KP overall. Research is needed to establish causality and develop interventions.

Gordon, D. B., De Leon-Casasola, O. A., Wu, C. L., Sluka, K. A., Brennan, T. J., & Chou, R. (2016).

Research gaps in practice guidelines for acute postoperative pain management in adults: Findings

from a review of the evidence for an American Pain Society clinical practice guideline. *Journal of Pain*, 17(2), 158-166.

Acute postoperative pain is a common clinical condition that, when poorly controlled, can result in a number of significant negative consequences. The American Pain Society commissioned an evidence-based guideline on the management of postoperative pain to promote evidence-based, safe, and effective perioperative pain management. An interdisciplinary panel developed 31 key questions and inclusion criteria to guide the evidence review. Investigators reviewed 6556 abstracts from multiple electronic databases up to November 2012, an updated evidence review to October 2014, and key references suggested by expert reviewers. More than 800 primary studies not included in a systematic review and 107 systematic reviews were included. Despite a large body of evidence, a number of critical research gaps were identified where only low-quality or insufficient evidence was found to help guide clinical practice recommendations. This report identifies evidence gaps including optimal methods and timing of perioperative patient education, nonpharmacological modalities, combinations of analgesic techniques, monitoring of patient response to treatment, techniques for neuraxial and regional analgesia, and organizational care delivery models. Recommendations to help guide the design of future perioperative studies are offered. Perspective Acute postoperative pain is a common clinical condition requiring an evidence-based, planned, and multimodal approach. Despite the plethora of published evidence, much of it is weak and key questions remain unanswered. Researchers are encouraged to work together to produce strong evidence to help guide clinical decisions in perioperative pain management. © 2016 American Pain Society.

Gordon, M. J., Danilova, O., Spurgeon, S., & Danilov, A. (2016). Cardiac non-hodgkin lymphoma: Clinical characteristics and trends in survival. *European Journal of Haematology*,
OBJECTIVES: Describe the clinical characteristics and outcomes in cardiac Non-Hodgkin lymphoma (NHL). METHODS: A retrospective analysis of 94 cases of NHL with biopsy-proven cardiac involvement in PubMed between 1990 and 2015. RESULTS: Among cases with cardiac involvement, diffuse large B-cell lymphoma was the most common histologic subtype (58%), followed by T-cell lymphoma (16%), Burkitt lymphoma (9%) and small lymphocytic lymphoma (6%). Symptomatic heart failure was the most common clinical presentation (34%), 20% of

patients had no cardiac symptoms. Median survival was 3 months (range, 0-72) among all patients. Patients who presented with heart failure had inferior outcomes. Patients with primary, vs secondary, cardiac involvement had a trend towards superior outcomes. Importantly, chemotherapy treatment was associated with a prolongation in median survival (18 vs 1 month, HR 0.16, 95% CI, 0.47-0.54, $p=0.0003$), and patients diagnosed in the chemo-immunotherapy era demonstrated a trend toward better outcomes. Median survival was not reached among patients with B-cell malignancies who were alive at one month after the diagnosis..

CONCLUSION: Pathologic lymphomatous involvement of cardiac tissue should be considered in the evaluation of patients with NHL.. Durable remissions can be achieved in B-cell NHL with cardiac involvement, and thus therapy should be considered in such cases. This article is protected by copyright. All rights reserved.

Greco, M. F., Frieden, I. J., Drolet, B. A., Garzon, M. C., Mancini, A. J., Chamlin, S. L., et al. (2016).

Infantile hemangiomas in twins: A prospective cohort study. *Pediatric Dermatology*,

Background: Twins have a higher-than-expected risk of infantile hemangiomas (IHs), but the exact reasons for this association are not clear. Comparing concordant and discordant twin pairs might help elucidate these factors and yield more information about IH risk factors. Methods: A prospective cohort study of twin pairs from 12 pediatric dermatology centers in the United States, Canada, Argentina, and Spain was conducted. Information regarding maternal pregnancy history, family history of vascular birthmarks, zygosity (if known), and pregnancy-related information was collected. Information regarding twins ($N = 202$ sets) included birthweight, gestational age (GA), presence or absence of IHs, numbers and subtypes of IHs, presence of other birthmarks, and other medical morbidities. Results: Two hundred two sets of twins were enrolled. Concordance for IH was present in 37% of twin pairs. Concordance for IH was inversely related to gestational age (GA), present in 42% of GA of 32 weeks or less, 36% of GA of 33 to 36 weeks, and 32% of GA of 37 weeks or more. Twins of GA of 34 weeks or less were more than two and a half times as likely to be concordant as those of GA of 35 weeks or more (odds ratio (OR) = 2.66, 95% confidence interval (CI) = 1.42-4.99; $p < 0.01$). In discordant twins, lower birthweight conferred a high risk of IH; of the 64 sets of twins with 10% or greater difference in weight, the smaller twin had IH in 62.5% ($n = 40$) of cases, versus 37.5% ($n = 24$) of cases in which the higher-birthweight twin

was affected. Zygosity was reported in 188 twin sets (93%). Of these, 78% were dizygotic and 22% monozygotic. There was no statistically significant difference in rates of concordance between monozygotic twins (43%, 18/42) and dizygotic twins (36%, 52/146) ($p = 0.50$). In multivariate analysis comparing monozygotic and dizygotic twins, adjusting for effects of birthweight and sex, the likelihood of concordance for monozygotic was not appreciably higher than that for dizygotic twins (OR = 1.14, 95% CI = 0.52-2.49). Female sex also influenced concordance, confirming the effects of female sex on IH risk. The female-to-male ratio was 1.7:1 in the entire cohort and 1.9:1 in those with IH. Of the 61 concordant twin sets with known sex of both twins, 41% were female/female, 43% were female/male, and 16% were male/male. Conclusions: These findings suggest that the origin of IHs is multifactorial and that predisposing factors such as birthweight, sex, and GA may interact with one another such that a threshold is reached for clinical expression. © 2016 Wiley Periodicals, Inc.

Greenberg, G. D., & Trainor, B. C. (2015). Sex differences in the social behavior network and mesolimbic dopamine system. (pp. 77-106) Elsevier Inc.

Sexual selection is based on differential investment in reproduction by males and females, and in most species of vertebrates females invest more energy in each individual offspring than males. Neurobiological systems controlling social behaviors have thus evolved under some form of sexual selection for millions of years. An evolutionarily conserved social behavior network consisting of hypothalamic and limbic brain nuclei contains several regions that are sexually dimorphic. Intriguingly, even nodes within this network that are not sexually dimorphic play a key role in mediating sex differences in behavior. In contrast, little anatomical sexual dimorphism is observed within the mesolimbic dopamine system. Nonetheless, important sex differences in dopamine functions have been identified. This chapter will review sex differences in the structure and function of these circuits and examine how social experience acting on these circuits induces long-term changes in behavior. © 2016 Elsevier Inc. All rights reserved.

Grobman, W. A., Bailit, J., Lai, Y., Reddy, U. M., Wapner, R. J., Varner, M. W., et al. (2016).

Association of the duration of active pushing with obstetric outcomes. *Obstetrics and Gynecology*, 127(4), 667-673.

OBJECTIVE: To estimate the associations between the duration of active pushing during the second stage of labor and maternal and neonatal outcomes. METHODS: We performed an observational study in which data were obtained by trained abstractors from maternal and neonatal charts of deliveries at 25 hospitals over a 3-year period. In this secondary analysis, women with no prior cesarean delivery who had a term, singleton, cephalic gestation and reached complete dilation were analyzed. The duration of pushing, defined as the time from initiation of pushing to either vaginal delivery or the decision to proceed with a cesarean delivery, was determined. The primary maternal outcome was cesarean delivery and the primary neonatal outcome was a composite that included: mechanical ventilation, proven sepsis, brachial plexus palsy, clavicular fracture, skull fracture, other fracture, seizures, hypoxic-ischemic encephalopathy, or death. Nulliparous and parous women were analyzed separately in univariable and then multivariable analyses. RESULTS: A total of 53,285 women were analyzed. In both nulliparous and parous women, longer duration of pushing was associated with increased odds of both cesarean delivery and the neonatal adverse outcome composite. Nevertheless, even after 4 hours of pushing, approximately 78% of nulliparous women who continued with active pushing had a vaginal delivery and more than 97% did not have the composite adverse neonatal outcome. Similarly, after more than 2 hours of pushing, approximately 82% of parous women who continued active pushing delivered vaginally and more than 97% did not have the adverse neonatal outcome. CONCLUSION: A longer duration of pushing is associated with an increased relative risk, but small absolute difference in risk, of neonatal complications. Approximately 78% of nulliparous women delivered vaginally even after 4 hours of pushing.

Gross, S. M., & Lehman, S. L. (2016). Functional phosphorylation sites in cardiac myofilament proteins are evolutionarily conserved in skeletal myofilament proteins. *Physiological Genomics*, , physiolgenomics.00112.2015.

Protein phosphorylation plays an important role in regulating cardiac contractile function, but phosphorylation is not thought to play a regulatory role in skeletal muscle. To examine how myofilament phosphorylation arose in the human heart, we analyzed the amino acid sequences of 25 cardiac phosphorylation sites in animals ranging from fruit flies to humans. These analyses indicated that of the 25 human phosphorylation sites examined, 11 have been conserved across

vertebrates and four have been sporadically present in vertebrates. Furthermore, all 11 of the cardiac sites found across vertebrates were present in skeletal muscle isoforms, along with three sites that was sporadically present. Based on the conservation of amino acid sequences between cardiac and skeletal contractile proteins, we tested for phosphorylation in mammalian skeletal muscle using several biochemical techniques and found evidence that multiple myofilament proteins were phosphorylated. Several of these phosphorylation sites were validated using mass spectrometry, including one site that is present in slow and fast twitch TnI, but was lost in cardiac TnI. Thus, several myofilament phosphorylation sites present in the human heart likely arose in invertebrate muscle, have been evolutionarily conserved in skeletal muscle, and potentially have functional effects in both skeletal and cardiac muscle.

Gunderson, A. J., Kaneda, M. M., Tsujikawa, T., Nguyen, A. V., Affara, N. I., Ruffell, B., et al. (2016). Bruton tyrosine kinase-dependent immune cell cross-talk drives pancreas cancer. *Cancer Discovery*, 6(3), 270-285.

Pancreas ductal adenocarcinoma (PDAC) has one of the worst 5-year survival rates of all solid tumors, and thus new treatment strategies are urgently needed. Here, we report that targeting Bruton tyrosine kinase (BTK), a key B-cell and macrophage kinase, restores T cell-dependent antitumor immune responses, thereby inhibiting PDAC growth and improving responsiveness to standard-of-care chemotherapy. We report that PDAC tumor growth depends on cross-talk between B cells and FcR γ ⁺ tumor-associated macrophages, resulting in TH2-type macrophage programming via BTK activation in a PI3K γ -dependent manner. Treatment of PDAC-bearing mice with the BTK inhibitor PCI32765 (ibrutinib) or by PI3K γ inhibition reprogrammed macrophages toward a TH1 phenotype that fostered CD8⁺ T-cell cytotoxicity, and suppressed PDAC growth, indicating that BTK signaling mediates PDAC immunosuppression. These data indicate that pharmacologic inhibition of BTK in PDAC can reactivate adaptive immune responses, presenting a new therapeutic modality for this devastating tumor type. SIGNIFICANCE: We report that BTK regulates B-cell and macrophage-mediated T-cell suppression in pancreas adenocarcinomas. Inhibition of BTK with the FDA-approved inhibitor ibrutinib restores T cell-dependent antitumor immune responses to inhibit PDAC growth and improves responsiveness to chemotherapy,

presenting a new therapeutic modality for pancreas cancer. © 2015 American Association for Cancer Research.

Gupta, M. P., Chan, R. V. P., Anzures, R., Ostmo, S., Jonas, K., & Chiang, M. F. (2016). Practice patterns in retinopathy of prematurity treatment for disease milder than recommended by guidelines. *American Journal of Ophthalmology*, 163, 1-10.

Purpose To characterize the frequency of and clinical indications for which experts treat retinopathy of prematurity (ROP) milder than type 1 disease, the recommended threshold for treatment from established consensus guidelines. Design Descriptive analysis. Methods setting: Multicenter. study population: A database of 1444 eyes generated prospectively from all babies screened for ROP at 1 of 6 major ROP centers whose parents provided informed consent. intervention: Retrospective review of the database and charts to identify all patients treated for ROP milder than type 1. main outcome measure: Indication(s) for treatment. Results A total of 137 eyes of 70 infants were treated for ROP. Of these 137 eyes, 13 (9.5%) were treated despite a clinical diagnosis milder than type 1 ROP. Indications for treatment included active ROP with the fellow eye being treated for type 1 ROP (2 eyes, 15.4%); concerning structural changes (9 eyes, 69.2%), including tangential traction with temporal vessel straightening concerning for macular dragging (8 eyes, 61.5%) and thick stage 3 membranes with anteroposterior traction concerning for progression to stage 4 ROP (3 eyes, 23.1%); persistent ROP at an advanced postmenstrual age (4 eyes, 30.8%); and/or vitreous hemorrhage (3 eyes, 23.1%). Conclusions Experts in this study occasionally recommended treatment in eyes with disease less than type 1 ROP. This study has important clinical implications and highlights the role of individual clinical judgment in situations not covered by evidence-based treatment guidelines. © 2016 Elsevier Inc. ALL RIGHTS RESERVED.

Haisley, K. R., Hart, K. D., Fischer, L. E., Kunio, N. R., Bakis, G., Tieu, B. H., et al. (2016). Increasing tumor length is associated with regional lymph node metastases and decreased survival in esophageal cancer. *American Journal of Surgery*,
BACKGROUND: Although tumor length has received little attention for staging of esophageal cancer, it may be a valid prognostic feature for node positivity and survival. METHODS: Through

retrospective review of a prospective institutional database, esophageal cancer patients who completed esophagectomy without neoadjuvant chemoradiation were analyzed. Pathologic tumor lengths were compared with node positivity and survival through a zero-inflated negative binomial regression model and multivariable Cox proportional hazards model, respectively. RESULTS: Between January 2000 and July 2015, 98 patients met inclusion, criteria (84% male, median age of 65, 90% adenocarcinoma). Median tumor length was 2.5 cm with each 1-cm increase in length increasing the odds of node positivity (odds ratio 3.55, 95% confidence interval 1.50 to 8.40, $P = .004$) and decreasing overall survival (hazards ratio 1.18, 95% confidence interval 1.06 to 1.32, $P < .003$). CONCLUSION: This study suggests an association among tumor length, lymph node metastasis, as well as overall survival in esophageal cancer patients who have not received neoadjuvant chemoradiotherapy.

Hansen, K. F., Sakamoto, K., Aten, S., Snider, K. H., Loeser, J., Hesse, A. M., et al. (2016). Targeted deletion of miR-132/-212 impairs memory and alters the hippocampal transcriptome. *Learning and Memory*, 23(2), 61-71.

miR-132 and miR-212 are structurally related microRNAs that have been found to exert powerful modulatory effects within the central nervous system (CNS). Notably, these microRNAs are tandemly processed from the same noncoding transcript, and share a common seed sequence: thus it has been difficult to assess the distinct contribution of each microRNA to gene expression within the CNS. Here, we employed a combination of conditional knockout and transgenic mouse models to examine the contribution of the miR-132/-212 gene locus to learning and memory, and then to assess the distinct effects that each microRNA has on hippocampal gene expression. Using a conditional deletion approach, we show that miR-132/-212 double-knockout mice exhibit significant cognitive deficits in spatial memory, recognition memory, and in tests of novel object recognition. Next, we utilized transgenic miR-132 and miR-212 overexpression mouse lines and the miR-132/-212 double-knockout line to explore the distinct effects of these two miRNAs on the transcriptional profile of the hippocampus. Illumina sequencing revealed that miR-132/-212 deletion increased the expression of 1138 genes; Venn analysis showed that 96 of these genes were also downregulated in mice overexpressing miR-132. Of the 58 genes that were decreased in animals overexpressing miR-212, only four of them were also increased in the knockout line.

Functional gene ontology analysis of downregulated genes revealed significant enrichment of genes related to synaptic transmission, neuronal proliferation, and morphogenesis, processes known for their roles in learning, and memory formation. These data, coupled with previous studies, firmly establish a role for the miR-132/-212 gene locus as a key regulator of cognitive capacity. Further, although miR-132 and miR-212 share a seed sequence, these data indicate that these miRNAs do not exhibit strongly overlapping mRNA targeting profiles, thus indicating that these two genes may function in a complex, nonredundant manner to shape the transcriptional profile of the CNS. The dysregulation of miR-132/-212 expression could contribute to signaling mechanisms that are involved in an array of cognitive disorders. © 2016 Eaton et al.

Hansen, M., O'Brien, K., Meckler, G., Chang, A. M., & Guise, J. M. (2016). Understanding the value of mixed methods research: The children's safety initiative-emergency medical services. *Emergency Medicine Journal : EMJ*,

Mixed methods research has significant potential to broaden the scope of emergency care and specifically emergency medical services investigation. Mixed methods studies involve the coordinated use of qualitative and quantitative research approaches to gain a fuller understanding of practice. By combining what is learnt from multiple methods, these approaches can help to characterise complex healthcare systems, identify the mechanisms of complex problems such as medical errors and understand aspects of human interaction such as communication, behaviour and team performance. Mixed methods approaches may be particularly useful for out-of-hospital care researchers because care is provided in complex systems where equipment, interpersonal interactions, societal norms, environment and other factors influence patient outcomes. The overall objectives of this paper are to (1) introduce the fundamental concepts and approaches of mixed methods research and (2) describe the interrelation and complementary features of the quantitative and qualitative components of mixed methods studies using specific examples from the Children's Safety Initiative-Emergency Medical Services (CSI-EMS), a large National Institutes of Health-funded research project conducted in the USA.

Harrington, E. K., Dworkin, S., Withers, M., Onono, M., Kwena, Z., & Newmann, S. J. (2016).

Gendered power dynamics and women's negotiation of family planning in a high HIV prevalence setting: A qualitative study of couples in western Kenya. *Culture, Health and Sexuality*, 18(4), 453-469.

In sub-Saharan Africa, high burdens of HIV and unmet need for contraception often coexist. Research emphasises the need to engage men and couples in reproductive health, yet couples' negotiations around fertility and family planning in the context of HIV have been sparsely studied. This study examined the gendered power dynamics that frame women's and couples' negotiations of contraceptive use in western Kenya. We conducted 76 in-depth interviews with 38 couples, of whom 22 couples were concordant HIV-positive. Qualitative data were analysed using a grounded theory approach. Direct communication around contraception with men was often challenging due to perceived or expressed male resistance. A substantial minority of women avoided male reproductive decision-making authority through covert contraceptive use, with concern for severe consequences when contraceptive use was discovered. Many men assumed that family planning use signified female promiscuity and that infidelity motivated covert use. Men were more willing to use condoms to avoid HIV re-infection or on the recommendation of HIV care providers, which allowed some women leverage to insist on condom use. Our findings highlight the tension between male dominated reproductive decision making and women's agency and point to the need for gender transformative approaches seeking to challenge masculinities that negatively impact health. © 2015 Taylor & Francis.

Hayden, D., Chang, Y. H., Goncalves, J., & Tomlin, C. J. (2016). Sparse network identifiability via compressed sensing. *Automatica*, 68, 9-17.

The problem of identifying sparse solutions for the link structure and dynamics of an unknown linear, time-invariant network is posed as finding sparse solutions x to $Ax=b$. If the matrix A satisfies a rank condition, this problem has a unique, sparse solution. Here each row of A comprises one experiment consisting of input/output measurements and cannot be freely chosen. We show that if experiments are poorly designed, the rank condition may never be satisfied, resulting in multiple solutions. We discuss strategies for designing experiments such that A has the desired properties and the problem is therefore well posed. This formulation allows prior

knowledge to be taken into account in the form of known nonzero entries of x , requiring fewer experiments to be performed. Simulated examples are given to illustrate the approach, which provides a useful strategy commensurate with the type of experiments and measurements available to biologists. We also confirm suggested limitations on the use of convex relaxations for the efficient solution of this problem. © 2016 Elsevier Ltd. All rights reserved.

He, G. -, & Taggart, D. P. (2016). Spasm in arterial grafts in coronary artery bypass grafting surgery. *Annals of Thoracic Surgery*, *101*(3), 1222-1229.

Spasm of arterial grafts in coronary artery bypass grafting surgery is still a clinical problem, and refractory spasm can occasionally be lethal. Perioperative spasm in bypass grafts and coronary arteries has been reported in 0.43% of all coronary artery bypass grafting surgery, but this may be an underestimate. Spasm can develop not only in the internal mammary artery but more frequently in the right gastroepiploic and radial artery. The mechanism of spasm can involve many pathways, particularly those involving regulation of the intracellular calcium concentration. Endothelial dysfunction also plays a role in spasm. Depending on the clinical scenario, the possibility of spasm during and after coronary artery bypass grafting should be confirmed by angiography. If present, immediate intraluminal injection of vasodilators is often effective, although other procedures such as an intraaortic balloon pump or extracorporeal membrane oxygenation may also become necessary to salvage the patient. Prevention of spasm involves many considerations, and the principles are discussed in this review article. © 2016 The Society of Thoracic Surgeons.

Henderson, R. M., Lovato, L., Miller, M. E., Fielding, R. A., Church, T. S., Newman, A. B., et al. (2016). Effect of statin use on mobility disability and its prevention in at-risk older adults: The LIFE study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*,
BACKGROUND: HMG-CoA reductase inhibitors (statins) are among the most commonly prescribed classes of medications. Although their cardiovascular benefits and myalgia risks are well documented, their effects on older adults initiating an exercise training program are less understood. METHODS: 1,635 sedentary men and women aged 70-89 years with Short Physical Performance Battery (SPPB) score of 9 or below and were able to walk 400 m were randomized

to a structured, moderate-intensity physical activity (PA) program consisting of both center-based (twice/wk) and home-based (3-4 times/wk) aerobic, resistance, and flexibility training or to a health education (HE) program combined with upper extremity stretching. RESULTS: Overall, the PA intervention was associated with lower risk of major mobility disability (hazard ratio [HR] = 0.82; 95% confidence interval [CI] = 0.69-0.98). The effect was similar (p value for interaction = .62) in both statin users (PA n = 415, HE n = 412; HR = 0.86, 95% CI = 0.67-1.1) and nonusers (PA n = 402, HE n = 404; HR = 0.78, 95% CI = 0.61-1.01). Attendance was similar for statin users (65%) and nonusers (63%). SPPB at 12 months was slightly greater for PA (8.35+/-0.10) than for HE (7.94+/-0.10) in statin users but not in nonusers (PA 8.25+/-0.10, HE 8.16+/-0.10), though the interaction effect was not statistically significant. Self-reported PA levels were not different between statin users and nonusers. CONCLUSIONS: Although statins have been associated with adverse effects on muscle, data from the LIFE Study show that statin users and nonusers both benefit from PA interventions. Older adults who require statin medications to manage chronic medical conditions and are sedentary will be able to benefit from interventions to increase PA.

Hermes, S. M., Andresen, M. C., & Aicher, S. A. (2016). Localization of TRPV1 and P2X3 in unmyelinated and myelinated vagal afferents in the rat. *Journal of Chemical Neuroanatomy*, 72, 1-7.

The vagus nerve is dominated by afferent fibers that convey sensory information from the viscera to the brain. Most vagal afferents are unmyelinated, slow-conducting C-fibers, while a smaller portion are myelinated, fast-conducting A-fibers. Vagal afferents terminate in the nucleus tractus solitarius (NTS) in the dorsal brainstem and regulate autonomic and respiratory reflexes, as well as ascending pathways throughout the brain. Vagal afferents form glutamatergic excitatory synapses with postsynaptic NTS neurons that are modulated by a variety of channels. The organization of vagal afferents with regard to fiber type and channels is not well understood. In the present study, we used tract tracing methods to identify distinct populations of vagal afferents to determine if key channels are selectively localized to specific groups of afferent fibers. Vagal afferents were labeled with isolectin B4 (IB4) or cholera toxin B (CTb) to detect unmyelinated and myelinated afferents, respectively. We find that TRPV1 channels are

preferentially found in unmyelinated vagal afferents identified with IB4, with almost half of all IB4 fibers showing co-localization with TRPV1. These results agree with prior electrophysiological findings. In contrast, we found that the ATP-sensitive channel P2X3 is found in a subset of both myelinated and unmyelinated vagal afferent fibers. Specifically, 18% of IB4 and 23% of CTb afferents contained P2X3. The majority of CTb-ir vagal afferents contained neither channel. Since neither channel was found in all vagal afferents, there are likely further degrees of heterogeneity in the modulation of vagal afferent sensory input to the NTS beyond fiber type. © 2015 Elsevier B.V..

Hessell, A. J., Jaworski, J. P., Epton, E., Matsuda, K., Pandey, S., Kahl, C., et al. (2016). Early short-

term treatment with neutralizing human monoclonal antibodies halts SHIV infection in infant macaques. *Nature Medicine*,

Prevention of mother-to-child transmission (MTCT) of HIV remains a major objective where antenatal care is not readily accessible. We tested HIV-1-specific human neutralizing monoclonal antibodies (NmAbs) as a post-exposure therapy in an infant macaque model for intrapartum MTCT. One-month-old rhesus macaques were inoculated orally with the simian-human immunodeficiency virus SHIVSF162P3. On days 1, 4, 7 and 10 after virus exposure, we injected animals subcutaneously with NmAbs and quantified systemic distribution of NmAbs in multiple tissues within 24 h after antibody administration. Replicating virus was found in multiple tissues by day 1 in animals that were not treated. All NmAb-treated macaques were free of virus in blood and tissues at 6 months after exposure. We detected no anti-SHIV T cell responses in blood or tissues at necropsy, and no virus emerged after CD8+ T cell depletion. These results suggest that early passive immunotherapy can eliminate early viral foci and thereby prevent the establishment of viral reservoirs.

Hessell, A. J., Malherbe, D. C., Pissani, F., McBurney, S., Krebs, S. J., Gomes, M., et al. (2016).

Achieving potent autologous neutralizing antibody responses against tier 2 HIV-1 viruses by strategic selection of envelope immunogens. *Journal of Immunology (Baltimore, Md.: 1950)*, 196(7), 3064-3078.

Advancement in immunogen selection and vaccine design that will rapidly elicit a protective Ab

response is considered critical for HIV vaccine protective efficacy. Vaccine-elicited Ab responses must therefore have the capacity to prevent infection by neutralization-resistant phenotypes of transmitted/founder (T/F) viruses that establish infection in humans. Most vaccine candidates to date have been ineffective at generating Abs that neutralize T/F or early variants. In this study, we report that coimmunizing rhesus macaques with HIV-1 gp160 DNA and gp140 trimeric protein selected from native envelope gene sequences (envs) induced neutralizing Abs against Tier 2 autologous viruses expressing cognate envelope (Env). The Env immunogens were selected from envs emerging during the earliest stages of neutralization breadth developing within the first 2 years of infection in two clade B-infected human subjects. Moreover, the IgG responses in macaques emulated the targeting to specific regions of Env known to be associated with autologous and heterologous neutralizing Abs developed within the human subjects. Furthermore, we measured increasing affinity of macaque polyclonal IgG responses over the course of the immunization regimen that correlated with Tier 1 neutralization. In addition, we report firm correlations between Tier 2 autologous neutralization and Tier 1 heterologous neutralization, as well as overall TZM-bl breadth scores. Additionally, the activation of Env-specific follicular helper CD4 T cells in lymphocytes isolated from inguinal lymph nodes of vaccinated macaques correlated with Tier 2 autologous neutralization. These results demonstrate the potential for native Env derived from subjects at the time of neutralization broadening as effective HIV vaccine elements.

Hildebran, C., Leichtling, G., Irvine, J. M., Cohen, D. J., Hallvik, S. E., & Deyo, R. A. (2016). Clinical styles and practice policies: Influence on communication with patients regarding worrisome prescription drug monitoring program data. *Pain Medicine (Malden, Mass.)*,

OBJECTIVES: Clinician communication with patients regarding worrisome findings in Prescription Drug Monitoring Programs (PDMPs) may influence patient responses and subsequent care. The authors studied the range of approaches clinicians report when communicating with patients in this situation and how practice policies and procedures may influence this communication.

DESIGN: Qualitative interviews of clinician PDMP users. SETTING: Oregon registrants in the state's PDMP. SUBJECTS: Thirty-three clinicians practicing in pain management, emergency medicine, primary care, psychiatry, dentistry, and surgery. METHODS: The authors conducted

semi-structured interviews via telephone with clinicians who routinely used the PDMP. A multidisciplinary team used a grounded theory approach to identify ways clinicians reported using information from the PDMP when communicating with patients, and policies that influenced that communication. RESULTS: Clinicians reported using a range of approaches for communicating about PDMP results, from openly sharing, to questioning patients without disclosing access to the PDMP, to avoiding the conversation. Clinicians also reported practice policies and procedures that influenced communication with their patients about prescribing and ongoing care, including policies that normalized use of the PDMP with all patients and those that facilitated difficult conversations by providing a rationale not to prescribe in certain circumstances. CONCLUSION: Clinicians' self-reported approaches to sharing PDMP findings and communicating prescribing decisions with patients vary and may be facilitated by appropriate practice policies. Such communication may have implications for patient engagement and alliance building. More research is needed to identify best practices and potential guidelines for effectively communicating about PDMP findings, as this may enhance health outcomes.

Hoffman, B. D., Barnes, M., Ferrell, C., Gellin, C., Lichtenstein, C., Donnelly, J., et al. (2016). The community health and advocacy milestones profile (CHAMP): A novel tool linking community pediatrics and advocacy training to assessment of milestones-based competence in pediatric residency training. *Academic Pediatrics*,

Holihan, J. L., Bondre, I., Askenasy, E. P., Greenberg, J. A., Keith, J. N., Martindale, R. G., et al. (2016). Sublay versus underlay in open ventral hernia repair. *Journal of Surgical Research*, 202(1), 26-32.

Background The ideal location for mesh placement in open ventral hernia repair (OVHR) remains under debate. Current trends lean toward underlay or sublay repair. We hypothesize that in patients undergoing OVHR, sublay versus underlay placement of mesh results in fewer surgical site infections (SSIs) and recurrences. Materials and methods A multi-institution database of all OVHRs performed from 2010 to 2011 was accessed. Patients with mesh placed in the sublay or underlay position and at least 1 mo of follow-up were included. Primary outcome was SSI. Secondary outcome was hernia recurrence. Multivariate analysis was performed using logistic

regression for SSI and Cox regression for recurrence. Subgroup analysis of elective, midline ventral incisional hernias was also performed. Results Of 447 patients, 139 (31.1%) had a sublay repair. The unadjusted analysis showed no difference in SSI and lower recurrence using sublay compared with underlay. On multivariate analysis, there was no difference in SSI using sublay compared with underlay (odds ratio 1.5, 95% confidence interval CI] 0.8-2.8). Recurrence was less common with sublay (hazard ratio 0.4, 95% CI 0.2-0.8). On subgroup analysis of elective, midline incisional hernias only (n = 247), there were more SSIs with sublay compared with underlay repair (28.0% versus 15.1%, P = 0.018); however, there was no difference in major SSI (sublay 9.3% versus underlay 5.8%, P = 0.315). There were fewer recurrences using sublay repair compared with underlay repair (10.7% versus 25.0%, P = 0.010). Conclusions In this multi-center, risk-adjusted study, sublay repair was associated with fewer recurrences than underlay repair and no difference in SSI. Randomized controlled trials are warranted to validate these findings. © 2016 Elsevier Inc. All rights reserved.

Holliday, E. B., Dieckmann, N. F., McDonald, T. L., Hung, A. Y., Thomas, C. R., & Wood, L. J. (2016).

Relationship between fatigue, sleep quality and inflammatory cytokines during external beam radiation therapy for prostate cancer: A prospective study. *Radiotherapy and Oncology*, 118(1), 105-111.

Background and purpose Mechanisms of fatigue reported during radiotherapy are poorly defined but may include inflammatory cytokines and/or sleep disturbances. This prospective, longitudinal, phase II study assessed fatigue, sleep, and serum cytokine levels during radiotherapy for early-stage prostate cancer (PCa). Material and methods Twenty-eight men undergoing radiotherapy for early-stage PCa wore an Actiwatch Score to record fatigue level, sleep time, onset latency, efficiency and wake after sleep onset. Serum levels of IL-1 α , IL-1 β , TNF- α , IL-6, IL-8, IL-10 and VEGF were measured weekly during radiotherapy. Patient reported quality of life (QOL) metrics were collected before and after treatment. Linear mixed effects models examined trajectories across treatment weeks. Results Fatigue increased across treatment weeks (P <.01), and fatigue was associated with decreased patient-reported QOL. Sleep efficiency increased across treatment weeks (rate of change over time =.29, P =.03), and sleep onset latency decreased (rate of change over time =.86, P =.06). IL-6 tended to increase during treatment (P

= 0.09), but none of the cytokine levels or sleep variables were significantly related to fatigue trajectories. Conclusions Despite increased sleep efficiency across treatment weeks, fatigue significantly increased. Although IL-6 increased during the course of radiotherapy, cytokines levels were not associated with fatigue scores or sleep disturbance. Further studies are needed to define the mechanisms for fatigue during radiotherapy. © 2015 Elsevier Ireland Ltd. All rights reserved. *Radiotherapy and Oncology* 118 (2016) 105111.

Hope, E. R., Mhawech-Fauceglia, P., Pejovic, T., Zahn, C. M., Wang, G., Conrads, T. P., et al. (2016).

Nestin: A biomarker of aggressive uterine cancers. *Gynecologic Oncology*, 140(3), 503-511.

Objective Evidence of potential prognostic and predictive value for nestin was investigated in well-annotated uterine cancers (UCs). Methods Nestin expression and previously-published biomarkers were evaluated by immunohistochemistry (IHC) in UC tissue microarrays. Biomarkers were categorized as low vs. high, and nestin was cut at 10% positive staining. Relationship between nestin and clinicopathologic factors, biomarkers and outcome were evaluated using exact/log-rank testing or logistic/Cox modeling. Results There were 323 eligible cases, 34% had advanced stage disease, 37% had type II disease, and 5% were carcinosarcomas. High nestin, observed in 19% of cases, was more common in advanced vs. early stage disease, type II cancers or uterine carcinosarcoma vs. type I cancers, grade 3 disease, positive lymphovascular space invasion (LVSI) and tumors > 6 cm ($p < 0.05$). Nestin was inversely correlated with ER, PR and TFF3, and correlated with p53 and IMP3. Women with high vs. low nestin had worse progression-free survival (PFS) and cancer-specific survival overall, and worse PFS in the subset who received no adjuvant therapy or radiation, or had early stage, type I disease or tumors with both low and high ER, PR, TFF3, PTEN, p53 or IMP3. The relationship between nestin and PFS was independent of stage, LVSI and risk categorization but not type of UC. Conclusions High nestin was more common in UCs with aggressive features and poor outcome. Nestin may represent a predictive biomarker for treatment selection for patients previously considered to be lower risk and a candidate for no or radiation-based adjuvant therapy, and compliment ER/PR testing. © 2016 Elsevier Inc. All rights reserved.

Hugos, C. L., Frankel, D., Tompkins, S. A., & Cameron, M. (2016). Community delivery of a comprehensive fall-prevention program in people with multiple sclerosis: A retrospective observational study. *International Journal of MS Care, 18*(1), 42-48.

BACKGROUND: People with multiple sclerosis (MS) fall frequently. In 2011, the National Multiple Sclerosis Society launched a multifactorial fall-prevention group exercise and education program, Free From Falls (FFF), to prevent falls in MS. The objective of this study was to assess the impact of participation in the FFF program on balance, mobility, and falls in people with MS. METHODS: This was a retrospective evaluation of assessments from community delivery of FFF. Changes in Activities-specific Balance Confidence scale scores, Berg Balance Scale scores, 8-foot Timed Up and Go performance, and falls were assessed. RESULTS: A total of 134 participants completed the measures at the first and last FFF sessions, and 109 completed a 6-month follow-up assessment. Group mean scores on the Activities-specific Balance Confidence scale ($F_{1,66} = 17.14, P < .05, \eta^2(2) = 0.21$), Berg Balance Scale ($F_{1,68} = 23.39, P < .05, \eta^2(2) = 0.26$), and 8-foot Timed Up and Go ($F_{1,79} = 4.83, P < .05, \eta^2(2) = 0.06$) all improved significantly from the first to the last session. At the 6-month follow-up, fewer falls were reported ($\chi^2(2) [4, N = 239] = 10.56, P < .05, \Phi = 0.21$). CONCLUSIONS: These observational data suggest that the FFF group education and exercise program improves balance confidence, balance performance, and functional mobility and reduces falls in people with MS.

Huguet, N., & Devoe, J. E. (2015). Suicide prevention in primary care medicine. *Mayo Clinic Proceedings, 90*(11), 1459-1461.

Huisman, C., Van, D. W., Schokker, M., Blancafort, P., Terpstra, M. M., Kok, K., et al. (2016). Re-expression of selected epigenetically silenced candidate tumor suppressor genes in cervical cancer by TET2-directed demethylation. *Molecular Therapy, 24*(3), 536-547.

DNA hypermethylation is extensively explored as therapeutic target for gene expression modulation in cancer. Here, we re-activated hypermethylated candidate tumor suppressor genes (TSGs) (C13ORF18, CCNA1, TFPI2, and Maspin) by TET2-induced demethylation in cervical cancer cell lines. To redirect TET2 to hypermethylated TSGs, we engineered zinc finger proteins (ZFPs), which were first fused to the transcriptional activator VP64 to validate effective gene re-

expression and confirm TSG function. ChIP-Seq not only revealed enriched binding of ZFPs to their intended sequence, but also considerable off-target binding, especially at promoter regions. Nevertheless, results obtained by targeted re-expression using ZFP-VP64 constructs were in line with cDNA overexpression; both revealed strong growth inhibition for C13ORF18 and TFPI2, but not for CCNA1 and Maspin. To explore effectivity of locus-targeted demethylation, ZFP-TET2 fusions were constructed which efficiently demethylated genes with subsequent gene re-activation. Moreover, targeting TET2 to TFPI2 and C13ORF18, but not CCNA1, significantly decreased cell growth, viability, and colony formation in cervical cancer cells compared to a catalytically inactive mutant of TET2. These data underline that effective re-activation of hypermethylated genes can be achieved through targeted DNA demethylation by TET2, which can assist in realizing sustained re-expression of genes of interest. © 2016 The American Society of Gene & Cell Therapy.

Ingelse, K., & Messecar, D. (2016). Rural women veterans' use and perception of mental health services. *Archives of Psychiatric Nursing, 30*(2), 244-248.

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

included episodes of chronic sexual harassment and ridicule, traumatic sexual assaults, and difficult combat experiences. Efforts to report mistreatment were unsuccessful or met with punishment. All the women interviewed reported that they would not have sought services without the help of a supportive peer who encouraged seeking care. Barriers to seeking care included feeling like they were not really a combat veteran (in spite of serving in a combat unit in Iraq); feeling stigmatized by providers and other military personnel, being treated as crazy; and a lack of interest from those providing care in hearing their stories. This study may generate positive social change by helping providers approach women veterans in a way that is sympathetic to their experiences.

Irani, M., Seifer, D. B., Grazi, R. V., Julka, N., Bhatt, D., Kalgi, B., et al. (2015). Vitamin D supplementation decreases TGF- β 1 bioavailability in PCOS: A randomized placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism*, 100(11), 4307-4314.

Context: There is an abnormal increase in TGF- β 1 bioavailability in women with polycystic ovary syndrome (PCOS), which might play a role in the pathophysiology of this syndrome.

VitaminD(VD) supplementation improves various clinical manifestations of PCOS and decreases TGF- β 1 levels in several diseases including myelofibrosis. Objective: The objective of the study was to determine the effect of VD supplementation on TGF- β 1 bioavailability in VD-deficient women with PCOS and assess whether changes in TGF- β 1/soluble endoglin (sENG) levels correlate with an improvement in PCOS clinical manifestations. Design: This was a prospective, randomized, placebo-controlled trial. Setting: The study was conducted at an academic-affiliated medical center. Participants: Sixty-eight VD-deficient women with PCOS who were not pregnant or taking any exogenous hormones were recruited between October 2013 and January 2015. Interventions: Forty-five women received 50 000 IU of oral vitamin D3 and 23 women received oral placebo once weekly for 8 weeks. Main Outcomes Measures: Serum TGF- β 1, sENG, lipid profile, testosterone, dehydroepiandrosterone sulfate, and insulin resistance were measured. The clinical parameters were evaluated before and 2 months after treatment. Results: The VD level significantly increased and normalized after VD supplementation (16.3 ± 0.9 [SEM] to 43.2 ± 2.4 ng/mL; $P < .01$), whereas it did not significantly change after placebo. After the VD supplementation, there was a significant decrease in the following: the interval between

menstrual periods (80 ± 9 to 60 ± 6 d; $P < .04$), Ferriman-Gallwey score ($9.8-1.5$ to $8.1-1.5$; $P < .01$), triglycerides (138 ± 22 to 117 ± 20 mg/dL; $P = .03$), and TGF- β 1 to sENG ratio (6.7 ± 0.4 to 5.9 ± 0.4 ; $P = .04$). In addition, the Δ TGF- β 1 to sENG ratio was positively correlated with Δ triglycerides ($r = 0.59$; $P = .03$). Conclusions: VD supplementation in VD-deficient women with PCOS significantly decreases the bioavailability of TGF- β 1, which correlates with an improvement in some abnormal clinical parameters associated with PCOS. This is a novel mechanism that could explain the beneficial effects of VD supplementation in women with PCOS. These findings may support new treatment modalities for PCOS, such as the development of anti-TGF- β drugs.

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Isenberg, J. Y., Quinones, A. R., Slatore, C. G., Bryson, W. C., & Thielke, S. M. (2016). Trends in cigarette smoking and cessation among medicare managed care recipients, 2005-2012. *Addictive Behaviors, 58*, 155-160.

OBJECTIVES: To examine recent trends in cigarette smoking among older (65 years and above) adults in the United States. METHODS: We used data from the Medicare Health Outcomes Survey dataset to estimate rates of smoking, quitting, and (re)starting from 2005 to 2012. Medicare Advantage enrollees completed mail surveys at baseline and two years later. We included subgroup analyses by sex, race, and self-rated health. RESULTS: Smoking prevalence declined slightly, with most of the decline occurring over the course of a single year (2007-2008). Rates of quitting declined slightly (meaning fewer people were quitting), and (re)starting marginally declined from 2005 to 2012. There were no substantial differences between subgroups. We did not observe any significant changes in prevalence or cessation of smoking among Medicare Advantage participants during this time. CONCLUSIONS: Smoking remains a public health problem for older adults. We did not find evidence of significant changes in smoking prevalence or cessation for older adults during the time period we examined.

Jacoby, V. L., Kohi, M. P., Poder, L., Jacoby, A., Lager, J., Schembri, M., et al. (2016). PROMISE trial: A pilot, randomized, placebo-controlled trial of magnetic resonance guided focused ultrasound for uterine fibroids. *Fertility and Sterility, 105*(3), 773-780.

Objective To evaluate the feasibility of a full-scale placebo-controlled trial of magnetic resonance-

guided focused ultrasound for fibroids (MRgFUS) and obtain estimates of safety and efficacy. Design Pilot, randomized, placebo-controlled trial. Setting University medical center. Patient(s) Premenopausal women with symptomatic uterine fibroids. Intervention(s) Participants randomized in a 2:1 ratio to receive MRgFUS or placebo procedure. Main Outcome Measure(s) Primary outcome: change in fibroid symptoms from baseline to 4 and 12 weeks after treatment assessed by the Uterine Fibroid Symptom Quality of Life Questionnaire (UFS-QOL); secondary outcome: incidence of surgery or procedures for recurrent symptoms at 12 and 24 months. Result(s) Twenty women with a mean age of 44 years ($\hat{\pm}$ standard deviation 5.4 years) were enrolled, and 13 were randomly assigned to MRgFUS and 7 to placebo. Four weeks after treatment, all participants reported improvement in the UFS-QOL: a mean of 10 points in the MRgFUS group and 9 points in the placebo group (for difference in change between groups). By 12 weeks, the MRgFUS group had improved more than the placebo group (mean 31 points and 13 points, respectively). The mean fibroid volume decreased 18% in the MRgFUS group with no decrease in the placebo group at 12 weeks. Two years after MRgFUS, 4 of 12 women who had a follow-up evaluation (30%) had undergone another fibroid surgery or procedure. Conclusion(s) Women with fibroids were willing to enroll in a randomized, placebo-controlled trial of MRgFUS. A placebo effect may explain some of the improvement in fibroid-related symptoms observed in the first 12 weeks after MRgFUS. © 2016 American Society for Reproductive Medicine.

Jain, A., Lafage, V., Kelly, M. P., Hassanzadeh, H., Neuman, B. J., Sciubba, D. M., et al. (2016).

Validity, reliability, and responsiveness of SRS-7 as an outcomes assessment instrument for operatively treated patients with adult spinal deformity. *Spine*,

STUDY DESIGN: Retrospective analysis OBJECTIVE.: The aim of our study was to compare the normality, concurrent validity, internal consistency, responsiveness, and dimensionality of an item response theory-derived 7-question instrument (SRS-7), against the Scoliosis Research Society-22r (SRS-22r) questionnaire in operatively treated patients with adult spinal deformity (ASD). SUMMARY OF BACKGROUND DATA: Compared with SRS-22r, SRS-7 (which has been validated in operatively treated patients with adolescent idiopathic scoliosis) has advantages of being short, unidimensional, and linear. METHODS: A prospective database of ASD patients was queried for patients 18 years or older who were operatively treated, and who answered pre- and

postoperative (at 2-year follow-up) SRS-22r questions (n = 276). Corresponding SRS-7 scores were calculated using answers to SRS-22r items 1, 4, 6, 10, 18, 19, and 20. Significance was set at a P value less than 0.01. RESULTS: SRS-7 and SRS-22r were normally distributed preoperatively but not postoperatively. SRS-7 and SRS-22r scores had high correlation both preoperatively (r = 0.76, P < 0.01) and postoperatively (r = 0.83, P < 0.01). The internal consistency reliability Cronbach alpha values were 0.61 (SRS-7) and 0.83 (SRS-22r) preoperatively and 0.91 (SRS-7) and 0.95 (SRS-22r) postoperatively. SRS-7 was found to be more responsive than SRS-22r with measures of effect size: Cohen d = 1.21 versus 1.13, Hedge g = 1.21 versus 1.13, and effect size correlation r = 0.52 versus 0.49. Iterative principal factor analysis of pre- and postoperative scores showed the presence of 1 dominant latent factor in SRS-7 (unidimensionality) and 4 latent factors in SRS-22r (multidimensionality). CONCLUSION: SRS-7 is a valid, reliable, responsive, and unidimensional instrument, which can be used as a short-form alternative to the SRS-22r for assessing global changes in patient-reported outcomes over time in patients with ASD. LEVEL OF EVIDENCE: 3.

Jamal, S. A., Arampatzis, S., Harrison, S. L., Bucur, R. C., Ensrud, K., Orwoll, E. S., et al. (2015). Hyponatremia and fractures: Findings from the MrOS study. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, 30(6), 970-975.

Hyponatremia may be a risk factor for fracture. To determine the relationship between hyponatremia and fracture we conducted cross-sectional and longitudinal analyses using data from the Osteoporotic Fractures in Men (MrOS) study. The MrOS study enrolled 5122 community dwelling men aged ≥ 65 years from six centers across the United States. We excluded men taking bisphosphonates, those with unknown medication history, those without serum sodium measures, or those with out of range assays for serum sodium. Serum sodium was measured at study entry. Subjects were followed for fractures (nonspine [including hip], hip, incident morphometric, and prevalent morphometric) for up to 9 years. We used Cox proportional hazards models to analyze the association between serum sodium levels (≥ 135 mmol/L) and risk of nonspine and hip fractures, with results presented as hazard ratios (HRs) and 95% confidence intervals (CIs). We examined the association between morphometric vertebral fractures and

serum sodium using logistic regression models, presented as odds ratios (ORs) and 95% CI. Hyponatremia was observed in 64 men (1.2% of the cohort). After adjusting for age, BMI, study center, and other covariates, we found that, compared to men with serum sodium ≥ 135 mmol/L, those with serum sodium < 135 mmol/L, had an increased risk of hip fracture (HR = 3.04; 95% CI, 1.37 to 6.75), prevalent morphometric spine fracture (OR = 2.46; 95% CI, 1.22 to 4.95), and incident morphometric spine fracture (OR = 3.53; 95% CI, 1.35 to 9.19), but not nonspine fracture (OR = 1.44; 95% CI, 0.85 to 2.44). Adjusting for bone mineral density (BMD) did not change our findings. Our data show that hyponatremia is associated with up to a doubling in the risk of hip and morphometric spine fractures, independent of BMD. Further studies, to determine how hyponatremia causes fractures and if correction of hyponatremia decreases fractures, are needed.

Jansen, L. A., Mahadevan, D., Appelbaum, P. S., Klein, W. M., Weinstein, N. D., Mori, M., et al.

(2016). Dispositional optimism and therapeutic expectations in early-phase oncology trials. *Cancer*,

BACKGROUND: Prior research has identified unrealistic optimism as a bias that might impair informed consent among patient-subjects in early-phase oncology trials. However, optimism is not a unitary construct; it also can be defined as a general disposition, or what is called dispositional optimism. The authors assessed whether dispositional optimism would be related to high expectations for personal therapeutic benefit reported by patient-subjects in these trials but not to the therapeutic misconception. The authors also assessed how dispositional optimism related to unrealistic optimism. **METHODS:** Patient-subjects completed questionnaires designed to measure expectations for therapeutic benefit, dispositional optimism, unrealistic optimism, and the therapeutic misconception. **RESULTS:** Dispositional optimism was found to be significantly associated with higher expectations for personal therapeutic benefit (Spearman rank correlation coefficient [r], 0.333; $P < .0001$), but was not associated with the therapeutic misconception (Spearman r, -0.075; $P = .329$). Dispositional optimism was found to be weakly associated with unrealistic optimism (Spearman r, 0.215; $P = .005$). On multivariate analysis, both dispositional optimism ($P = .02$) and unrealistic optimism ($P < .0001$) were found to be independently associated with high expectations for personal therapeutic benefit. Unrealistic optimism ($P =$

.0001), but not dispositional optimism, was found to be independently associated with the therapeutic misconception. CONCLUSIONS: High expectations for therapeutic benefit among patient-subjects in early-phase oncology trials should not be assumed to result from misunderstanding of specific information regarding the trials. The data from the current study indicate that these expectations are associated with either a dispositionally positive outlook on life or biased expectations concerning specific aspects of trial participation. Not all manifestations of optimism are the same, and different types of optimism likely have different consequences for informed consent in early-phase oncology research. © 2016 American Cancer Society.

Jaqaman, K., Galbraith, J. A., Davidson, M. W., & Galbraith, C. G. (2016). Changes in single-molecule integrin dynamics linked to local cellular behavior. *Molecular Biology of the Cell*,
Recent advances in light microscopy permit visualization of the behavior of individual molecules within dense macromolecular ensembles in live cells. It is now conceptually possible to relate the dynamic organization of molecular machinery to cellular function. However, inherent heterogeneities as well as disparities between spatial and temporal scales pose substantial challenges in deriving such a relationship. New approaches are required to link discrete single molecule behavior with continuous cellular-level processes. Here we combined intercalated molecular and cellular imaging with a computational framework to detect reproducible transient changes in the behavior of individual molecules that are linked to cellular behaviors. Applying our approach to integrin transmembrane receptors revealed a spatial density gradient underlying characteristic molecular density increases and mobility decreases indicating the subsequent onset of local protrusive activity. Integrin mutants further revealed that these density and mobility transients are separable and depend upon different binding domains within the integrin cytoplasmic tail. We propose that our approach provides a generalizable paradigm for dissecting dynamic spatiotemporal molecular behaviors that are linked to local cellular events.

Jayaram, H., Strouthidis, N. G., & Kamal, D. S. (2016). Trabeculectomy for normal tension glaucoma: Outcomes using the moorfields safer surgery technique. *British Journal of Ophthalmology*, *100*(3), 332-338.

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

glaucoma (NTG) with contemporary surgical techniques. Methods Retrospective consecutive, non-comparative case series of 131 eyes of 98 patients undergoing trabeculectomy between 2007 and 2013 in a dedicated NTG clinic. Data collected during routine clinical care were analysed. Assessment of clinical outcomes included intraocular pressure (IOP) reduction, bleb function, final visual acuity, evidence of glaucoma progression, postoperative complications and further surgical intervention. Surgical failure was defined as a failure to meet specified IOP-related criteria, the need to undergo further glaucoma surgery for raised IOP or loss of light perception vision. A further analysis was also performed which considered failure as glaucoma progression following surgery. Outcomes were evaluated using Kaplan-Meier life-table analysis. Results The cumulative percentages of unqualified success as defined by a $\geq 30\%$ reduction of IOP from baseline preoperative maximum (95% CI; IOP of all eyes: mean \pm SD) at 1, 2, 3 and 4 years after surgery were 91.1% (84.1% to 95.1%; 9.7 ± 2.9 mm Hg), 74.1% (63.7% to 81.8%; 10.3 ± 3.0 mm Hg), 64.8% (52.7% to 74.6%; 10.6 ± 2.5 mm Hg) and 62.1% (49.3% to 72.6%; 10.2 ± 2.1 mm Hg), respectively. At 2 years of follow-up there was no significant association between either previous cataract surgery or ethnicity and failure. Cumulative percentages of unqualified success at 4 years after surgery as defined by a filtering trabeculectomy bleb or absence of glaucoma progression were 91.6% (83.2% to 95.9%) and 92.3% (81.3% to 97.0%), respectively. Postoperative complications such as early (2.3%) and late (0.8%) hypotony were significantly lower than suggested by the current literature. Conclusions Trabeculectomy in NTG patients undertaken using contemporary surgical techniques and intensive postoperative management is associated with more successful long-term outcomes and fewer complications than the currently available literature suggests.

Jelin, A. C., Sharshiner, R., & Caughey, A. B. (2016). Maternal co-morbidities and neonatal outcomes associated with cystic fibrosis. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, , 1-15.

OBJECTIVE: To evaluate maternal co-morbidities and adverse perinatal outcomes associated with cystic fibrosis (CF). METHODS: This is a retrospective cohort study of 2,178,954 singleton pregnancies at ≥ 20 weeks' gestation with and without CF in the state of California during the

years 2005-2008. ICD-9 codes and linked hospital discharge and vital statistics data were utilized. Rates of maternal co-morbidities, fetal congenital anomalies and adverse perinatal outcomes were compared in those with CF and those without. Maternal co-morbidities included gestational hypertension, preeclampsia, gestational diabetes and primary cesarean delivery. Perinatal outcomes included neonatal demise, preterm birth, intrauterine growth restriction, macrosomia, anomaly, fetal demise, asphyxia, respiratory distress syndrome, jaundice, intraventricular hemorrhage, hypoglycemia and necrotizing enterocolitis. RESULTS: The cohort included 2,178,954 pregnancies of which 77 mothers had CF. Mothers with CF were more likely to have pre-gestational diabetes and had higher rates of primary cesarean delivery. Neonates delivered to mothers with cystic fibrosis were more likely to be born preterm and have congenital anomalies but otherwise were not at increased risk for significant neonatal morbidity or mortality when adjusted for gestational age. CONCLUSION: Mothers with CF are more likely to have pre-gestational diabetes, deliver preterm (<37 weeks gestation) and have a primary cesarean delivery. Infants are more likely to have congenital anomalies. In addition to early diabetic screening and genetic counseling, a detailed fetal anatomy ultrasound should be performed in women with CF.

John McConnell, K. (2016). Oregon's medicaid coordinated care organizations. *JAMA - Journal of the American Medical Association*, 315(9), 869-870.

Johnson, L. A., Zuloaga, K. L., Kugelman, T. L., Mader, K. S., Morr , J. T., Zuloaga, D. G., et al. (2016). Amelioration of metabolic syndrome-associated cognitive impairments in mice via a reduction in dietary fat content or infusion of non-diabetic plasma. *Ebiomedicine*, 3, 26-42. Obesity, metabolic syndrome (MetS) and type 2 diabetes (T2D) are associated with decreased cognitive function. While weight loss and T2D remission result in improvements in metabolism and vascular function, it is less clear if these benefits extend to cognitive performance. Here, we highlight the malleable nature of MetS-associated cognitive dysfunction using a mouse model of high fat diet (HFD)-induced MetS. While learning and memory was generally unaffected in mice with type 1 diabetes (T1D), multiple cognitive impairments were associated with MetS, including deficits in novel object recognition, cued fear memory, and spatial learning and memory.

However, a brief reduction in dietary fat content in chronic HFD-fed mice led to a complete rescue of cognitive function. Cerebral blood volume (CBV), a measure of vascular perfusion, was decreased during MetS, was associated with long term memory, and recovered following the intervention. Finally, repeated infusion of plasma collected from age-matched, low fat diet-fed mice improved memory in HFD mice, and was associated with a distinct metabolic profile. Thus, the cognitive dysfunction accompanying MetS appears to be amenable to treatment, related to cerebrovascular function, and mitigated by systemic factors. © 2015 The Authors.

Jordan, C. S., Minitzer, U., Yarbrough, K., & Mengden, S. J. (2016). Urticarial exanthem associated with capnocytophaga canimorsus bacteremia after a dog bite. *JAAD Case Reports*, 2(2), 98-101.

Juan De Solis, A., Baquero, A. F., Bennett, C. M., Grove, K. L., & Zeltser, L. M. (2016). Postnatal undernutrition delays a key step in the maturation of hypothalamic feeding circuits. *Molecular Metabolism*, 5(3), 198-209.

Objective: Humans and animals exposed to undernutrition (UN) during development often experience accelerated "catch-up" growth when food supplies are plentiful. Little is known about the mechanisms regulating early growth rates. We previously reported that actions of leptin and presynaptic inputs to orexigenic NPY/AgRP/GABA (NAG) neurons in the arcuate nucleus of the hypothalamus are almost exclusively excitatory during the lactation period, since neuronal and humoral inhibitory systems do not develop until after weaning. Moreover, we identified a critical step that regulates the maturation of electrophysiological responses of NAG neurons at weaning - the onset of genes encoding ATP-dependent potassium (KATP) channel subunits. We explored the possibility that UN promotes subsequent catch-up growth, in part, by delaying the maturation of negative feedback systems to neuronal circuits driving food intake. Methods: We used the large litter (LL) size model to study the impacts of postnatal UN followed by catch-up growth. We evaluated the maturation of presynaptic and postsynaptic inhibitory systems in NAG neurons using a combination of electrophysiological and molecular criteria, in conjunction with leptin's ability to suppress fasting-induced hyperphagia. Results: The onset of KATP channel subunit expression and function, the switch in leptin's effect on NAG neurons, the ingrowth of inhibitory inputs to NAG neurons, and the development of homeostatic feedback to feeding circuits were

delayed in LL offspring relative to controls. The development of functional KATP channels and the establishment of leptin-mediated suppression of food intake in the peri-weaning period were tightly linked and were not initiated until growth and adiposity of LL offspring caught up to controls. Conclusions: Our data support the idea that initiation of KATP channel subunit expression in NAG neurons serves as a molecular gatekeeper for the maturation of homeostatic feeding circuits. © 2016 The Authors.

Kabir, M. M., Ghafoori, E., & Tereshchenko, L. G. (2015). Assessment of joint interactions between respiration and baroreflex activity using joint symbolic dynamics in heart failure patients. *Computing in Cardiology*, 42, 809-812.

In this paper we employed a novel approach based on joint symbolic dynamics (JSD) to study interaction between respiratory phase and baroreflex activity. Electrocardiogram (ECG) and blood pressure recordings from six participants with history of heart failure were included in this study. First, the ECG R-peaks and systolic blood pressure indices were detected using parabolic fitting. Second, the respiratory signal was derived from Frank orthogonal ECG leads using QRS slopes and R-wave angles. Third, time series of R-R intervals and systolic blood pressure (SBP) were extracted, and respiratory phases were obtained using the Hilbert transform. Subsequently, each series was transformed into binary symbol vectors based on their successive changes and words of length '2' were formed. Baroreflex patterns were studied using word combinations representing baroreflex activity for specific changes in respiratory phases. Baroreflex activity was significantly higher for alternating low-high/high-low heart rate and SBP during inspiration as compared to continuous increase or decrease in heart rate and SBP ([Formula: see text], wRP=11: 39.1+/- 9.3% vs. [Formula: see text], wRP=11: 6.4+/-3.9%, $p < 0.0001$).

Kagan, R., Adams, J., Schulman, C., Laursen, R., Espana, K., Yoo, J., et al. (2016). What factors are associated with failure of compressive osseointegration fixation? *Clinical Orthopaedics and Related Research*,

BACKGROUND: Compressive osseointegration is as an alternative to traditional intramedullary fixation. Two- to 10-year survivorship and modes of failure have been reported; however, as a result of relatively small numbers, these studies are limited in their ability to identify risk factors

for failure. QUESTIONS/PURPOSES: (1) What is survivorship free from aseptic mechanical and survivorship free from overall failure of compressive osseointegration fixation? (2) What patient factors (age, sex, body mass index [BMI], anatomic location of reconstruction, indication for reconstruction, radiation, chemotherapy) are associated with increased risk of failure? METHODS: Between 2006 and 2014, surgeons at one center treated 116 patients with 137 Compress(R) implants for lower extremity oncologic reconstructions, revision arthroplasty, and fracture nonunion or malunion. One hundred sixteen implants were available for review with a minimum of 2-year followup (mean, 4 years; range, 2-9 years). Kaplan-Meier survival plots were produced to examine survivorship and Cox regression modeling was used to generate hazard ratios (HRs) for potential risk factors for failure. Patient factors (age, sex, BMI, anatomic location of reconstruction, indication for reconstruction, radiation, chemotherapy) were obtained from chart review and an institutional database. RESULTS: Survivorship free from aseptic mechanical failure was 95% (95% confidence interval [CI], 91%-99%) at 18 months and 93% (95% CI, 86%-99%) at 4 years. Survivorship free from overall failure was 82% (95% CI, 75%-89%) at 18 months and 75% (95% CI, 66%-84%) at 4 years. Risk of overall failure was increased with reconstruction of the proximal tibia (HR, 4.42; 95% CI 0.98-19.9) and distal femur (HR, 1.74; 95% CI, 0.50-6.09) compared to the proximal femur (HR, 1; referent; $p = 0.049$). Risk of aseptic mechanical failure was increased with reconstruction of the proximal tibia (HR, 1; referent) and distal femur (HR, 0.37; 95% CI, 0.08-1.77) compared with the proximal femur (HR, 0, $p = 0.048$). Radiation was associated with increased risk of overall failure (HR, 3.85; 95% CI, 1.84-8.02; $p < 0.003$), but not aseptic mechanical failure. Age, sex, BMI, chemotherapy, and surgical indication were not associated with increased risk of aseptic or overall failure. CONCLUSIONS: This study questions the use of age as a contraindication for the use of this technology and suggests this technology may be considered in proximal femoral reconstruction and for patients with indications other than primary oncologic reconstructions. Future research should establish long-term survivorship data to compare this approach with conventional intramedullary stems and to evaluate the potential benefits of preventing stress shielding and preserving bone stock in revision situations. LEVEL OF EVIDENCE: Level III, therapeutic study.

Kansagara, D., Chiovaro, J. C., Kagen, D., Jencks, S., Rhyne, K., O'Neil, M., et al. (2016). So many options, where do we start? an overview of the care transitions literature. *Journal of Hospital Medicine*, 11(3), 221-230.

BACKGROUND: Health systems are faced with a large array of transitional care interventions and patient populations to whom such activities might apply. PURPOSE: To summarize the health and utilization effects of transitional care interventions, and to identify common themes about intervention types, patient populations, or settings that modify these effects. DATA SOURCES: PubMed and Cochrane Database of Systematic Reviews (January 1950-May 2014), reference lists, and technical advisors. STUDY SELECTION: Systematic reviews of transitional care interventions that reported hospital readmission as an outcome. DATA EXTRACTION: We extracted transitional care procedures, patient populations, settings, readmissions, and health outcomes. We identified commonalities and compiled a narrative synthesis of emerging themes. DATA SYNTHESIS: Among 10 reviews of mixed patient populations, there was consistent evidence that enhanced discharge planning and hospital-at-home interventions reduced readmissions. Among 7 reviews in specific patient populations, transitional care interventions reduced readmission in patients with congestive heart failure and general medical populations. In general, interventions that reduced readmission addressed multiple aspects of the care transition, extended beyond hospital stay, and had the flexibility to accommodate individual patient needs. There was insufficient evidence on how caregiver involvement, transition to sites other than home, staffing, patient selection practices, or care settings modified intervention effects. CONCLUSIONS: Successful interventions are comprehensive, extend beyond hospital stay, and have the flexibility to respond to individual patient needs. The strength of evidence should be considered low because of heterogeneity in the interventions studied, patient populations, clinical settings, and implementation strategies. © 2016 Society of Hospital Medicine.

Karch, C. M., Ezerskiy, L. A., Bertelsen, S., Goate, A. M., Albert, M. S., Albin, R. L., et al. (2016).

Alzheimer's disease risk polymorphisms regulate gene expression in the ZCWPW1 and the CELF1 loci. *Plos One*, 11(2)

Late onset Alzheimer's disease (LOAD) is a genetically complex and clinically heterogeneous disease. Recent large-scale genome wide association studies (GWAS) have identified more than

twenty loci that modify risk for AD. Despite the identification of these loci, little progress has been made in identifying the functional variants that explain the association with AD risk. Thus, we sought to determine whether the novel LOAD GWAS single nucleotide polymorphisms (SNPs) alter expression of LOAD GWAS genes and whether expression of these genes is altered in AD brains. The majority of LOAD GWAS SNPs occur in gene dense regions under large linkage disequilibrium (LD) blocks, making it unclear which gene(s) are modified by the SNP. Thus, we tested for brain expression quantitative trait loci (eQTLs) between LOAD GWAS SNPs and SNPs in high LD with the LOAD GWAS SNPs in all of the genes within the GWAS loci. We found a significant eQTL between rs1476679 and PILRB and GATS, which occurs within the ZCWPW1 locus. PILRB and GATS expression levels, within the ZCWPW1 locus, were also associated with AD status. Rs7120548 was associated with MTCH2 expression, which occurs within the CELF1 locus. Additionally, expression of several genes within the CELF1 locus, including MTCH2, were highly correlated with one another and were associated with AD status. We further demonstrate that PILRB, as well as other genes within the GWAS loci, are most highly expressed in microglia. These findings together with the function of PILRB as a DAP12 receptor supports the critical role of microglia and neuroinflammation in AD risk. © 2016 Karch et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Karuppagounder, S. S., Xiong, Y., Lee, Y., Lawless, M. C., Kim, D., Nordquist, E., et al. (2016). LRRK2 G2019S transgenic mice display increased susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-mediated neurotoxicity. *Journal of Chemical Neuroanatomy*, Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common causes of late onset autosomal dominant form of Parkinson disease (PD). Gain of kinase activity due to the substitution of Gly 2019 to Ser (G2019S) is the most common mutation in the kinase domain of LRRK2. Genetic predisposition and environmental toxins contribute to the susceptibility of neurodegeneration in PD. To identify whether the genetic mutations in LRRK2 increase the susceptibility to environmental toxins in PD models, we exposed transgenic mice expressing human G2019S mutant or wild type (WT) LRRK2 to the environmental toxin 1-methyl-4-phenyl-

1,2,3,6-tetrahydropyridine (MPTP). MPTP treatment resulted in a greater loss of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta (SNpc) in LRRK2 G2019S transgenic mice compared to the LRRK2 WT overexpressing mice. Similarly loss of dopamine levels were greater in the striatum of LRRK2 G2019S mice when compared to the LRRK2 WT mice when both were treated with MPTP. This study suggests a likely interaction between genetic and environmental risk factors in the PD pathogenesis and that the G2019S mutation in LRRK2 increases the susceptibility of dopamine neurons to PD-causing toxins. © 2016 Elsevier B.V.

Kassakian, S. Z., Yackel, T. R., Deloughery, T., & Dorr, D. A. (2016). Clinical decision support reduces overuse of red blood cell transfusions: Interrupted time series analysis. *American Journal of Medicine,*

Background: Red blood cell transfusion is the most common procedure in hospitalized patients in the US. Growing evidence suggests that a sizeable percentage of these transfusions are inappropriate, putting patients at significant risk and increasing costs to the health care system.

Methods: We performed a retrospective quasi-experimental study from November 2008 until November 2014 in a 576-bed tertiary care hospital. The intervention consisted of an interruptive clinical decision support alert shown to a provider when a red blood cell transfusion was ordered in a patient whose most recent hematocrit was $\leq 21\%$. We used interrupted time series analysis to determine whether our primary outcome of interest, rate of red blood cell transfusion in patients with hematocrit $\leq 21\%$ per 100 patient (pt) days, was reduced by the implementation of the clinical decision support tool. The rate of platelet transfusions was used as a nonequivalent dependent control variable. Results: A total of 143,000 hospital admissions were included in our analysis. Red blood cell transfusions decreased from 9.4 to 7.8 per 100 pt days after the clinical decision support intervention was implemented. Interrupted time series analysis showed that significant decline of 0.05 (95% confidence interval CI], 0.03-0.07; $P < .001$) units of red blood cells transfused per 100 pt days per month was already underway in the preintervention period. This trend accelerated to 0.1 (95% CI, 0.09-0.12; $P < .001$) units of red blood cells transfused per 100 pt days per month following the implementation of the clinical decision support tool. There was no statistical change in the rate of platelet transfusion resulting from the intervention. Conclusions: The implementation of an evidence-based clinical decision

support tool was associated with a significant decline in the overuse of red blood cell transfusion. We believe this intervention could be easily replicated in other hospitals using commercial electronic health records and a similar reduction in overuse of red blood cell transfusions achieved. © 2016 Elsevier Inc.

Keller, F. S., Farsad, K., & Rosch, J. (2016). The transjugular intrahepatic portosystemic shunt: Technique and instruments. *Techniques in Vascular and Interventional Radiology*, 19(1), 2-9. Although transjugular intrahepatic portosystemic shunt (TIPS) was first described in 1971, it took 15 more years for technology, in the form of expandable metallic stents, to be developed to make TIPS a viable, widespread clinical procedure. Currently, expanded polytetrafluoroethylene-covered stent grafts that exhibit significantly greater long-term patency are used for TIPS creation by most interventionalists. TIPS creation requires specific interventional skills, tools, and devices for success. In the hands of skillful, experienced interventional radiologists, TIPS creation is performed safely and successfully in greater than 95% of cases.

Kim, E., Kim, J. S., Choi, M., & Thomas, C. R., Jr. (2016). Conditional survival in anal carcinoma using the national population-based survey of epidemiology and end results database (1988-2012). *Diseases of the Colon and Rectum*, 59(4), 291-298.

BACKGROUND: Conditional survival can provide valuable information for both patients and healthcare providers about the changing prognosis in surviving patients over time. OBJECTIVE: This study estimated conditional survival for patients with anal cancer in the United States through analysis of a national population-based cancer registry. DESIGN: Log-rank test identified significant covariates of cause-specific survival (defined as time from diagnosis until death from anal cancer). Significant covariates were considered in the multivariable regression of cause-specific survival using Cox proportional hazards models. SETTINGS: Covariates included cancer stage and demographic variables. PATIENTS: Patients in Surveillance, Epidemiology, and End Results regions diagnosed with anal squamous cell carcinoma as their first and only cancer diagnosis from 1988 to 2012 were selected from this database, and 5145 patients were included in the retrospective cohort study. MAIN OUTCOME MEASURE: Five-year conditional survival stratified by each variable in the final Cox models was measured RESULTS: : The final

multivariable models of overall and cause-specific survivals included stage, grade, sex, age, race, and relationship status. Over the first 6 years after diagnosis, conditional survival of distant stage increased from 37% to 89%, whereas regional stage increased from 65% to 93% and localized stage increased from 84% to 96%. The other variables had increasing prognosis as well, but the subgroups increased at a more similar rate over time. LIMITATIONS: The data source used does not include information on chemotherapy treatment, patient comorbidities, or socioeconomic status. CONCLUSIONS: Conditional survival showed improvement over time. Patients with advanced stage had the greatest improvement in conditional survival. This is the first study to provide specific conditional survival probabilities for patients with anal cancer.

Kim, G., Luján, R., Schwenk, J., Kelley, M. H., Aguado, C., Watanabe, M., et al. (2016). Membrane palmitoylated protein 2 is a synaptic scaffold protein required for synaptic SK2-containing channel function. *Elife*, 5

Mouse CA1 pyramidal neurons express apamin-sensitive SK2-containing channels in the post-synaptic membrane, positioned close to NMDA-type (N-methyl-D-aspartate) glutamate receptors. Activated by synaptically evoked NMDAR-dependent Ca²⁺ influx, the synaptic SK2-containing channels modulate excitatory post-synaptic responses and the induction of synaptic plasticity. In addition, their activity- and protein kinase A-dependent trafficking contributes to expression of long-term potentiation (LTP). We have identified a novel synaptic scaffold, MPP2 (membrane palmitoylated protein 2; p55), a member of the membrane-associated guanylate kinase (MAGUK) family that interacts with SK2-containing channels. MPP2 and SK2 co-immunopurified from mouse brain, and co-immunoprecipitated when they were co-expressed in HEK293 cells. MPP2 is highly expressed in the post-synaptic density of dendritic spines on CA1 pyramidal neurons. Knocking down MPP2 expression selectively abolished the SK2-containing channel contribution to synaptic responses and decreased LTP. Thus, MPP2 is a novel synaptic scaffold that is required for proper synaptic localization and function of SK2-containing channels. © Kim et al.

Kim, H. S., & Martin, T. M. (2016). *Genetics*. (pp. 115-122) Springer Berlin Heidelberg.

Uveitis is a broad term that is used to describe many distinct clinical syndromes. From the perspective of determining genetic risk factors for uveitis, having well-defined clinical phenotypes

is critical. Uveitis is typically classified on the basis of location, onset, symmetry, and relationship to associated systemic diseases. Clinical classifications of uveitis have been approached systematically with efforts made to standardize the relevant nomenclature. The ability to describe uveitis with universal assessment parameters is fundamental in defining phenotypic subsets useful for genetic studies. © Springer-Verlag Berlin Heidelberg 2016.

Kinast, R. M., Akula, K. K., Mansberger, S. L., Barker, G. T., Gardiner, S. K., Whitson, E., et al. (2016). Concentration accuracy of compounded mitomycin C for ophthalmic surgery. *JAMA Ophthalmology*, 134(2), 191-195.

IMPORTANCE Ophthalmologists rely on accurate concentrations of mitomycin C (MMC) to prevent scarring with trabeculectomy surgery. To our knowledge, the concentration accuracy and variability of compounded MMC are unknown. **OBJECTIVE** To determine whether the measured concentration differs from the expected concentration of 0.4mg/mL of MMC used in ophthalmic surgery. **DESIGN, SETTING, AND PARTICIPANTS** Laboratory experimental investigation conducted in July 2013. We acquired 60 samples of 0.4mg/mL of MMC from a spectrum of common compounding and storage techniques (refrigeration, freezing, and immediately compounded dry powder) and a variety of pharmacies (an academic hospital, a community hospital, and an independent Pharmacy Compounding Accreditation Board-accredited pharmacy). We used C18 reversed-phase high-performance liquid chromatography to measure the MMC concentration of all samples. We used pure MMC (Medisca Inc) to generate calibration curves and sulfanilamide as an internal standard. **MAIN OUTCOMES AND MEASURES** We calculated MMC concentration using a calibration curve (range, 0.3-0.5mg/mL) generated by dividing MMC peak area by internal standard peak area and plotting the area ratio against the calibrant concentrations. We compared the measured concentration against the expected 0.4mg/mL concentration for all samples. **RESULTS** Measurement of MMC using the high-performance liquid chromatography method demonstrated acceptable accuracy (92%-100%), precision (2%-6% coefficient of variation), and linearity (mean correlation coefficient of $r^2 = 0.99$). The measured MMC concentration determined using the high-performance liquid chromatography method for all samples was 12.5% lower than the expected 0.4mg/mL value (mean [SD], 0.35 [0.04]mg/mL; 95% CI, 0.34-0.36; $P > .001$) with a wide concentration range between 0.26 and 0.46mg/mL. **CONCLUSIONS**

AND RELEVANCE Common compounding and storage techniques for MMC resulted in a lower accuracy and wider range of concentration than expected. These differences in concentration may result from compounding techniques and/or MMC degradation. Variability in MMC concentration could cause inconsistency in glaucoma surgical results, but the clinical relevance of such findings on glaucoma surgery outcomes remains unknown. Copyright © 2016 American Medical Association. All rights reserved.

Klein, K. A., Watson, L., Ash, J. S., & Eden, K. B. (2016). Evaluation of risk communication in a mammography patient decision aid. *Patient Education and Counseling*,
Objectives: We characterized patients' comprehension, memory, and impressions of risk communication messages in a patient decision aid (PtDA), Mammopad, and clarified perceived importance of numeric risk information in medical decision making. Methods: Participants were 75 women in their forties with average risk factors for breast cancer. We used mixed methods, comprising a risk estimation problem administered within a pretest-posttest design, and semi-structured qualitative interviews with a subsample of 21 women. Results: Participants' positive predictive value estimates of screening mammography improved after using Mammopad. Although risk information was only briefly memorable, through content analysis, we identified themes describing why participants value quantitative risk information, and obstacles to understanding. We describe ways the most complicated graphic was incompletely comprehended. Conclusions: Comprehension of risk information following Mammopad use could be improved. Patients valued receiving numeric statistical information, particularly in pictograph format. Obstacles to understanding risk information, including potential for confusion between statistics, should be identified and mitigated in PtDA design. Practice implications: Using simple pictographs accompanied by text, PtDAs may enhance a shared decision-making discussion. PtDA designers and providers should be aware of benefits and limitations of graphical risk presentations. Incorporating comprehension checks could help identify and correct misapprehensions of graphically presented statistics. © 2016 Elsevier Ireland Ltd.

Kleven, M. D., Enns, C. A., & Zhang, A. -. (2016). Bone morphogenetic protein-6 mutations take their place in iron overload diseases. *Gastroenterology*, 150(3), 556-559.

Knupp, K. G., Coryell, J., Nickels, K. C., Ryan, N., Leister, E., Loddenkemper, T., et al. (2016).

Response to treatment in a prospective national infantile spasms cohort. *Annals of Neurology*, 79(3), 475-484.

Objective Infantile spasms are seizures associated with a severe epileptic encephalopathy presenting in the first 2 years of life, and optimal treatment continues to be debated. This study evaluates early and sustained response to initial treatments and addresses both clinical remission and electrographic resolution of hypsarrhythmia. Secondly, it assesses whether response to treatment differs by etiology or developmental status. Methods The National Infantile Spasms Consortium established a multicenter, prospective database enrolling infants with new diagnosis of infantile spasms. Children were considered responders if there was clinical remission and resolution of hypsarrhythmia that was sustained at 3 months after first treatment initiation. Standard treatments of adrenocorticotropic hormone (ACTH), oral corticosteroids, and vigabatrin were considered individually, and all other nonstandard therapies were analyzed collectively. Developmental status and etiology were assessed. We compared response rates by treatment group using chi-square tests and multivariate logistic regression models. Results Two hundred thirty infants were enrolled from 22 centers. Overall, 46% of children receiving standard therapy responded, compared to only 9% who responded to nonstandard therapy ($p < 0.001$). Fifty-five percent of infants receiving ACTH as initial treatment responded, compared to 39% for oral corticosteroids, 36% for vigabatrin, and 9% for other ($p < 0.001$). Neither etiology nor development significantly modified the response pattern by treatment group. Interpretation Response rate varies by treatment choice. Standard therapies should be considered as initial treatment for infantile spasms, including those with impaired development or known structural or genetic/metabolic etiology. ACTH appeared to be more effective than other standard therapies.

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Kondo, K. K., Damberg, C. L., Mendelson, A., Motu'apuaka, M., Freeman, M., O'Neil, M., et al. (2016).

Implementation processes and pay for performance in healthcare: A systematic review. *Journal of General Internal Medicine*, 31 Suppl 1, 61-69.

BACKGROUND: Over the last decade, various pay-for-performance (P4P) programs have been implemented to improve quality in health systems, including the VHA. P4P programs are

complex, and their effects may vary by design, context, and other implementation processes. We conducted a systematic review and key informant (KI) interviews to better understand the implementation factors that modify the effectiveness of P4P. METHODS: We searched PubMed, PsycINFO, and CINAHL through April 2014, and reviewed reference lists. We included trials and observational studies of P4P implementation. Two investigators abstracted data and assessed study quality. We interviewed P4P researchers to gain further insight. RESULTS: Among 1363 titles and abstracts, we selected 509 for full-text review, and included 41 primary studies. Of these 41 studies, 33 examined P4P programs in ambulatory settings, 7 targeted hospitals, and 1 study applied to nursing homes. Related to implementation, 13 studies examined program design, 8 examined implementation processes, 6 the outer setting, 18 the inner setting, and 5 provider characteristics. Results suggest the importance of considering underlying payment models and using statistically stringent methods of composite measure development, and ensuring that high-quality care will be maintained after incentive removal. We found no conclusive evidence that provider or practice characteristics relate to P4P effectiveness. Interviews with 14 KIs supported limited evidence that effective P4P program measures should be aligned with organizational goals, that incentive structures should be carefully considered, and that factors such as a strong infrastructure and public reporting may have a large influence. DISCUSSION: There is limited evidence from which to draw firm conclusions related to P4P implementation. Findings from studies and KI interviews suggest that P4P programs should undergo regular evaluation and should target areas of poor performance. Additionally, measures and incentives should align with organizational priorities, and programs should allow for changes over time in response to data and provider input.

Konishi, E., Nagai, T., Kobayashi, M., Mitsumori, Y., Ono, W., Asahara, K., et al. (2016). Post-fukushima radiation education for public health nursing students: A case study. *International Nursing Review*,

Background: The recent Fukushima Nuclear Power Plant accident was one of more than 200 serious nuclear/radiation incidents (accidents and disasters) that occurred worldwide since 1945. The current Fukushima disaster is in the recovery phase with the decreasing levels of radiation in the environment. However, fears and stigma related to the perceived risk of radiation exposure

persist among the general population. Introduction: To improve on students' preparedness for social and public health challenges after a radiation incidence, radiation education was provided for undergraduate public health nursing students. Aim: This case study reports the development and implementation of the first class of radiation education in public health nursing, as well as students' reflections on their class experience. Methods: We included a 90-min radiation class in an undergraduate public health nursing course in Tokyo, Japan. Lectures/discussion on technical and environmental aspects provided the minimally essential content for basic radiation knowledge. After class, all the 65 students were invited to freely write their reflections on the class. With their consent, 61 students' anonymous written accounts were qualitatively analysed. Results: Five themes emerged: awareness of ignorance about radiation, problems produced by the mass media, becoming knowledgeable about radiation, public health nurses' role, and trustful and enjoyable lecture. Discussion: The class inspired students to consider social, psychological and relational aspects of knowing and not knowing about radiation and their future professional role. Conclusion and implications for nursing: Once radiation is taught at school, nursing students will emerge as professionals with the belief that radiation is within their professional purview. Education is key to disaster prevention, preparation, response and recovery. Given the ubiquitous nature of health challenges after a radiation incident, radiation education is indispensable for nursing students worldwide. © 2016 International Council of Nurses.

Korfel, A., Chamberlain, M., Neuwelt, E., Thiel, E., Doolittle, N., Schlegel, U., et al. (2016). Therapy for secondary CNS involvement in malignant lymphomas: No standard yet! *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*,

Korkola, J. E., Heck, S., Olshen, A. B., Feldman, D. R., Reuter, V. E., Houldsworth, J., et al. (2015). Development and validation of a gene-based model for outcome prediction in germ cell tumors using a combined genomic and expression profiling approach. *Plos One*, 10(12)

Germ Cell Tumors (GCT) have a high cure rate, but we currently lack the ability to accurately identify the small subset of patients who will die from their disease. We used a combined genomic and expression profiling approach to identify genomic regions and underlying genes that are predictive of outcome in GCT patients. We performed arraybased comparative genomic

hybridization (CGH) on 53 non-seminomatous GCTs (NSGCTs) treated with cisplatin based chemotherapy and defined altered genomic regions using Circular Binary Segmentation. We identified 14 regions associated with two year disease-free survival (2yDFS) and 16 regions associated with five year disease-specific survival (5yDSS). From corresponding expression data, we identified 101 probe sets that showed significant changes in expression. We built several models based on these differentially expressed genes, then tested them in an independent validation set of 54 NSGCTs. These predictive models correctly classified outcome in 64-79.6% of patients in the validation set, depending on the endpoint utilized. Survival analysis demonstrated a significant separation of patients with good versus poor predicted outcome when using a combined gene set model. Multivariate analysis using clinical risk classification with the combined gene model indicated that they were independent prognostic markers. This novel set of predictive genes from altered genomic regions is almost entirely independent of our previously identified set of predictive genes for patients with NSGCTs. These genes may aid in the identification of the small subset of patients who are at high risk of poor outcome. © 2015 Korkola et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Kornegay, J. G., Leone, K. A., Wallner, C., Hansen, M., & Yarris, L. M. (2016). Development and implementation of an asynchronous emergency medicine residency curriculum using a web-based platform. *Internal and Emergency Medicine*,

The Residency Review Committee in Emergency Medicine requires residency programs to deliver at least 5 hours of weekly didactics. Achieving at least a 70 % average attendance rate per resident is required for residency program accreditation, and is used as a benchmark for residency graduation in our program. We developed a web-based, asynchronous curriculum to replace 1 hour of synchronous didactics, and hypothesized that the curriculum would be feasible to implement, well received by learners, and improve conference participation. This paper describes the feasibility and learner acceptability of a longitudinal asynchronous curriculum, and describes its impact on postgraduate year-1(PGY-1) resident conference participation and annual in-training examination scores. Using formal curriculum design methods, we developed modules

and paired assessment exercises to replace 1 hour of weekly didactics. We measured feasibility (development and implementation time and costs) and learner acceptability (measured on an anonymous survey). We compared pre- and post-intervention conference participation and in-service training examination scores using a two sample t test. The asynchronous curriculum proved feasible to develop and implement. PGY-1 resident conference participation improved compared to the pre-intervention year (85.6 vs. 62 %; 95 % CI 0.295-0.177; $p < 0.001$). We are unable to detect a difference between in-training examination results in either the PGY-1 group or across all residents by the introduction of this intervention. 18/31 (58 %) residents completed the post-intervention survey. 83 % reported satisfaction with curriculum changes. Strengths of the curriculum included clarity and timeliness of assignments. Weaknesses included technical difficulties with the online platform. Our curriculum is feasible to develop and implement. Despite technical difficulties, residents report high satisfaction with this new curriculum. Among PGY-1 residents there is improved conference participation compared to the prior year.

Korthuis, P. T., McGinnis, K. A., Kraemer, K. L., Gordon, A. J., Skanderson, M., Justice, A. C., et al. (2016). Quality of HIV care and mortality rates in HIV-infected patients. *Clinical Infectious Diseases*, 62(2), 233-239.

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 $\geq 80\%$ 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 $\geq 80\%$ 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 approximately 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 approximately 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. © 2015 The Author 2015. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail journals.permissions@oup.com.

Kouri, B. E., Abrams, R. A., Al-Refaie, W. B., Azad, N., Farrell, J., Gaba, R. C., et al. (2016). ACR appropriateness criteria radiologic management of hepatic malignancy. *Journal of the American College of Radiology : JACR*, 13(3), 265-273.

Management of primary and secondary hepatic malignancy is a complex problem. Achieving optimal care for this challenging population often requires the involvement of multiple medical and surgical disciplines. Because of the wide variety of potential therapies, treatment protocols for various malignancies continue to evolve. Consequently, development of appropriate therapeutic algorithms necessitates consideration of medical options, such as systemic chemotherapy; surgical options, such as resection or transplantation; and loco-regional therapies, such as thermal ablation and transarterial embolization techniques. This article provides a review of treatment strategies for the three most common subtypes of hepatic malignancy treated with loco-regional therapies: hepatocellular carcinoma, neuroendocrine metastases, and colorectal metastases. The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every three years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer reviewed journals and the application 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.

Kraakevik, J. (2016). Crafting a positive professional digital profile to augment your practice.

Neurology: Clinical Practice, 6(1), 87-93.

A digital profile is the sum content about a person on the Internet. A digital profile can be composed of personal or professional information shared on public Web sites posted personally or by others. One of the most effective ways to build a positive professional digital profile is through social media. It is increasingly important to maintain a positive digital profile as others mine the Internet to find out about a professional prior to meeting him or her. As the digital environment continues to grow, it will become increasingly difficult to neglect a professional digital profile without potential negative consequences. There are many benefits to creating a digital presence and using the tools available to learn about neurology and interact with other professionals and patients in ways that were not possible in the past. The spread of social media to a large part of the population makes it unlikely to go away. © 2016 American Academy of Neurology.

Ku, C. A., Ng, J. K., Karr, D. J., Reznick, L., Harding, C. O., Weleber, R. G., et al. (2016). Spectrum of ocular manifestations in cobalamin C and cobalamin A types of methylmalonic acidemia.

Ophthalmic Genetics, , 1-11.

Background: Cobalamin C disease (cbIC), which leads to methylmalonic acidemia with homocystinuria, is the most common inherited disorder of vitamin B12 metabolism. Reported ocular findings associated with cbIC have been maculopathy, pigmentary retinopathy, and optic nerve atrophy. Cobalamin A disease (cbIA) which causes an isolated methylmalonic acidemia without homocystinuria is rarer than cbIC. This is the first detailed report of the ocular findings associated with cbIA. We also describe the spectrum of ocular findings in our cbIC patients.

Materials and methods: A case series describing the ophthalmologic clinical course of six patients with a diagnosis of cobalamin C type and one patient with cobalamin A type of methylmalonic acidemia. Patients were diagnosed through biochemical laboratory testing and genetic analysis was conducted on most patients. Longitudinal fundus findings, optical coherence tomography (OCT), autofluorescence, and electrophysiology were followed in the patients. Results: The cbIA

patient demonstrated a relatively mild ocular phenotype with late-onset and slowly progressing temporal disc pallor and peripapillary atrophy in the second decade of life. The patient maintained good visual acuity and central vision, without evidence of maculopathy. The six cbIC patients demonstrated a range of ocular findings from unremarkable and mild phenotypes to significant retinopathy, including bull's eye maculopathy, severe maculopathy with punched out chorioretinal atrophy, peripheral bone spicules, and optic nerve atrophy. Conclusions: The spectrum of ocular manifestations seen with inherited disorders of cobalamin metabolism is wide, ranging from mild optic nerve atrophy to severe macular or retinal degeneration. This heterogeneity may in part reflect the associated biochemical phenotype, such as that observed between our cbIA and cbIC patients. We also observed heterogeneity within the cbIC type in agreement with previous reports. © 2016 Taylor & Francis

Kuhne, M. A., & Friess, D. (2016). Supine extensile approach to the anterolateral humerus.

Orthopedics, 39(1), e193-e195.

The radial nerve is at risk of injury during surgical approaches to the humeral shaft. Previous authors have described an anterolateral approach to the humerus limited by the radial nerve, requiring that distal dissection be carried anterior into a neurovascularly crowded interval. A novel extensile approach is described using a neuromuscular bridge to protect the radial nerve, thus enabling safe distal extension of the anterolateral humerus approach. The authors present a case series of 7 patients who required an extensile humeral exposure. To date, there have been no complications, including loss of reduction, malunion, nonunion, or nerve palsy. Copyright © SLACK Incorporated.

Kujovich, J. L. (2016). Evaluation of anemia. *Obstetrics and Gynecology Clinics of North America*,

Anemia is a common problem in primary care. Classification based on mean cell volume narrows the differential diagnosis and directs testing. A marked macrocytosis is characteristic of vitamin B12 and folate deficiencies, certain medications, and primary bone marrow disorders. The three most common causes of microcytic anemia are iron deficiency, thalassemia trait, and anemia of inflammation. Additional laboratory testing is required for diagnosis. Determination of the rate of development of anemia and examination of a blood smear may provide diagnostic clues to guide

more specialized testing. Diagnosis of iron, vitamin B12, or folate deficiency mandates determination of the underlying cause. © 2016 Elsevier Inc.

Langarani, M. S. E., Van Santen, J., Mohammadi, S. H., & Kain, A. (2015). Data-driven foot-based intonation generator for text-to-speech synthesis. *16th Annual Conference of the International Speech Communication Association, INTERSPEECH 2015, , 2015-January*. pp. 1596-1600.

We propose a method for generating F0 contours for text-to-speech synthesis. Training speech is automatically annotated in terms of feet, with features indicating start and end times of syllables, foot position, and foot length. During training, we fit a foot-based superpositional intonation model comprising accent curves and phrase curves. During synthesis, the method searches for stored, fitted accent curves associated with feet that optimally match to-be-synthesized feet in the feature space, while minimizing differences between successive accent curve heights. We tested the proposed method against the HMM-based Speech Synthesis System (HTS) by imposing contours generated by these two methods onto natural speech, and obtaining quality ratings. Test sets varied in how well they were covered by the training data. Contours generated by the proposed method were preferred over HTS-generated contours, especially for poorly-covered test items. To test the new method's usefulness for processing marked-up text input, we compared its ability to convey contrastive stress with that of natural speech recordings, and found no difference. We conclude that the new method holds promise for generating comparatively high-quality F0 contours, especially when training data are sparse and when mark-up is required. Copyright © 2015 ISCA.

Lanier, E. R., Foster, S., Brundage, T., Chou, S., Prichard, M. N., Kleiboeker, S., et al. (2016). Analysis of cytomegalovirus DNA polymerase gene mutations in a phase 2 clinical trial of brincidofovir prophylaxis. *The Journal of Infectious Diseases*,

Brincidofovir is an oral antiviral in development for prevention of cytomegalovirus disease. Cytomegalovirus genotyping from a phase 2 trial comparing brincidofovir with placebo for cytomegalovirus prophylaxis in hematopoietic cell transplant recipients provided initial data on the clinical resistance profile for brincidofovir. In this study, no known resistance-associated mutations were detected in brincidofovir-treated subjects; identified genotypic substitutions did

not confer resistance to cytomegalovirus antivirals in vitro, suggesting these changes represent polymorphisms unrelated to brincidofovir resistance. Lack of evidence for genotypic resistance during prophylaxis suggests that first-line use of brincidofovir for prevention of cytomegalovirus infection may preserve downstream options for patients.

Lau, D., Funao, H., Clark, A. J., Nicholls, F., Smith, J., Bess, S., et al. (2016). The clinical correlation of the hart-issg proximal junctional kyphosis severity scale with health-related quality-of-life outcomes and need for revision surgery. *Spine*, 41(3), 213-223.

Study Design. Retrospective analysis of prospective data. **Objective.** Evaluate the utility of the Hart-International Spine Study Group proximal junctional kyphosis severity scale (Hart-ISSG PJKSS). **Summary of Background Data.** Proximal junctional kyphosis (PJK) and failure (PJF) are well-described complications after long-segment instrumentation. The Hart-ISSG PJKSS was recently developed and incorporates neurological deficit, pain, instrumentation issues, degree of kyphosis, presence of fracture, and level of upper-most instrumented vertebrae. **Methods.** All adult spinal deformity patients with PJK or PJF were identified from two academic centers over a 7-year period. Health-related quality-of-life (HRQOL) outcomes were prospectively collected: Oswestry Disability Index (ODI), visual analogue scale (VAS) pain, SF-36 questionnaire, and SRS-30 questionnaire. Patients were retrospectively assigned Hart-ISSG PJKSS scores.

Correlation between the Hart-ISSG PJKSS and outcomes was assessed with linear regression, Pearson correlation coefficients, and χ^2 analysis. Results. A total of 184 cases were included; 21.2% were men and mean age was 65.0 years. Weakness and/or myelopathy were present in 11.4% of patients and 88.6% had pain. Instrumentation issues occurred in 44.0% and 64.1% had PJK-associated fractures. PJK occurred in the upper thoracic spine in 21.7% of cases. Mean PJKSS score was 5.9. The Hart-ISSG PJKSS was significantly and strongly associated with ODI ($P < 0.001$, $r = 0.611$), VAS pain ($P < 0.001$, $r = 0.676$), SRS-30 function ($P < 0.001$, $r = -0.401$), SRS-30 mental health ($P < 0.001$, $r = -0.592$), SRS-30 self-image ($P < 0.001$, $r = -0.511$), SRS-30 satisfaction ($P < 0.001$, $r = -0.531$), and SRS-30 pain ($P < 0.001$, $r = -0.445$). Higher scores were associated with higher proportion of patients undergoing revision surgery ($P < 0.001$); scores of 9 to 11 and 12 to 15 underwent revision 96.0% and 100.0% of the time, respectively. **Conclusion.** The Hart-ISSG PJKSS was strongly correlated with validated functional outcomes and higher

scores were associated with higher rates of revision surgery. The Hart-ISSG PJKSS may be a useful clinical tool in the treatment of patient with PJK. © 2016 Wolters Kluwer Health, Inc.

Leaverton, A., Lopes, V., Vohr, B., Dailey, T., Phipps, M. G., & Allen, R. H. (2016). Postpartum contraception needs of women with preterm infants in the neonatal intensive care unit. *Journal of Perinatology*, 36(3), 186-189.

Objectives:To evaluate postpartum contraception experiences of mothers with premature infants in the neonatal intensive care unit (NICU), their knowledge of risk factors for preterm delivery and their interest in a family planning clinic located near the NICU.**Study Design:**This is a cross-sectional survey of English or Spanish-speaking women 18 or older whose premature neonate had been in the NICU for 5 days or more in a current stable condition.**Results:**A total of 95 women were interviewed at a median of 2.7 weeks postpartum (range 0.6-12.9). Approximately 75% of women were currently using or planning to use contraception, with 33% using less effective methods. Half of women reported they would obtain contraception at a family planning clinic near the NICU. Only 32% identified a short interpregnancy interval as a risk factor for preterm delivery.**Conclusion:**Lack of knowledge of short interpregnancy interval as a risk factor for a future preterm delivery highlights the need to address postpartum contraception education and provision in this high-risk population. © 2016 Nature America, Inc.

Lee, E. J., Brown, B. R., Vance, E. E., Snow, P. E., Silver, P. B., Heinrichs, D., et al. (2016). Mincle activation and the Syk/Card9 signaling axis are central to the development of autoimmune disease of the eye. *Journal of Immunology (Baltimore, Md.: 1950)*, 196(7), 3148-3158.

Uveitis, which occurs in association with systemic immunological diseases, presents a considerable medical challenge because of incomplete understanding of its pathogenesis. The signals that initiate T cells to target the eye, which may be of infectious or noninfectious origin, are poorly understood. Experimental autoimmune uveoretinitis (EAU) develops in mice immunized with the endogenous retinal protein interphotoreceptor retinoid binding protein in the presence of the adjuvant CFA. EAU manifests as posterior ocular inflammation consisting of vasculitis, granulomas, retinal damage, and invasion of self-reactive T cells, which are key clinical features of human uveitis. Our studies uncover Card9 as a critical genetic determinant for EAU.

Card9 was responsible for Th17 polarization and Th17-associated Ag-specific responses, but not Th1-associated responses. Nonetheless, Card9 expression was essential for accumulation of both lineages within the eye. Consistent with its recently identified role as an intracellular signaling mediator for C-type lectin receptors (CLRs), a Card9-dependent transcriptional response in the neuroretina was observed involving genes encoding the CLRs Dectin-1, Dectin-2, and Mincle. Genetic deletion of these individual CLRs revealed an essential role for Mincle. Mincle activation was sufficient to generate the EAU phenotype, and this required activation of both Syk and Card9. In contrast, Dectin-1 contributed minimally and a possible repressive role was shown for Dectin-2. These findings extend our understanding of CLRs in autoimmune uveitis. The newly identified role of Mincle and Syk/Card9-coupled signaling axis in autoimmune uveitis could provide novel targets for treatment of patients with ocular inflammatory disease.

Liang, M. K., Holihan, J. L., Itani, K., Alawadi, Z. M., Gonzalez, J. R. F., Askenasy, E. P., et al. (2016).

Ventral hernia management: Expert consensus guided by systematic review. *Annals of Surgery*,
OBJECTIVE:: To achieve consensus on the best practices in the management of ventral hernias (VH). BACKGROUND:: Management patterns for VH are heterogeneous, often with little supporting evidence or correlation with existing evidence. METHODS:: A systematic review identified the highest level of evidence available for each topic. A panel of expert hernia-surgeons was assembled. Email questionnaires, evidence review, panel discussion, and iterative voting was performed. Consensus was when all experts agreed on a management strategy. RESULTS:: Experts agreed that complications with VH repair (VHR) increase in obese patients (grade A), current smokers (grade A), and patients with glycosylated hemoglobin (HbA1C) $\geq 6.5\%$ (grade B). Elective VHR was not recommended for patients with BMI ≥ 30 kg/m² (grade C), current smokers (grade A), or patients with HbA1C $\geq 8.0\%$ (grade B). Patients with BMI ≥ 30 kg/m² or HbA1C = 6.5–8.0% require individualized interventions to reduce surgical risk (grade C, grade B). Nonoperative management was considered to have a low-risk of short-term morbidity (grade C). Mesh reinforcement was recommended for repair of hernias ≥ 2 cm (grade A). There were several areas where high-quality data were limited, and no consensus could be reached, including mesh type, component separation technique, and management of complex patients. CONCLUSIONS:: Although there was consensus, supported by

grade Aâ€”C evidence, on patient selection, the safety of short-term nonoperative management, and mesh reinforcement, among experts; there was limited evidence and broad variability in practice patterns in all other areas of practice. The lack of strong evidence and expert consensus on these topics has identified gaps in knowledge where there is need of further evidence.

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Liko, J., Guzman-Cottrill, J., & Cieslak, P. R. (2016). Subacute sclerosing panencephalitis death â€” oregon, 2015. *Morbidity and Mortality Weekly Report*, 65(1), 10-11.

Lin, A. D., Miles, K., & Brinks, M. V. (2016). Prevalence of pterygia in hawaii: Examining cumulative surfing hours as a risk factor. *Ophthalmic Epidemiology*, , 1-5.

PURPOSE: To examine the association between surfing and pterygium prevalence in Hawaii.

METHODS: A convenience sampling was performed at four beaches on the island of Oahu, Hawaii. A total of 169 individuals were interviewed and underwent penlight examination to assess grade and extent of pterygium. RESULTS: Of 169 participants aged 18-80 years, 88 non-surfers, 41 occasional surfers, 15 recreational surfers and 25 surfing enthusiasts were identified based on their lifetime surfing hours. Overall, 19 participants were found to have pterygia (28 pterygia total) including two non-surfers (2.3%), five occasional surfers (12.2%), three recreational surfers (20.0%), and nine enthusiast surfers (36.0%). Variables associated with pterygium prevalence were lifetime surfing hours ($p < 0.0001$), outdoor occupation ($p = 0.04$), Hawaiian residence ($p = 0.009$), and Hawaiian/Pacific Islander ethnicity ($p = 0.002$). Multiple logistic regression with the outcome of pterygium was performed, along with multiple linear regression for the continuous outcomes of corneal extent, chord length, and apex-visual axis gap, with lifetime surfing hours as the primary explanatory variable. After adjustment for confounders, a significant linear relationship was observed between chord length and lifetime surfing hours ($p = 0.01$). CONCLUSION: Surfing was associated with an increased pterygium prevalence and trend towards an association with increased pterygium severity. Increased risk of exposure to wind, particle irritation, and ultraviolet (UV) radiation while surfing may contribute to pterygium development. Implications for public health include promoting UV protective eyewear during

surfing, in addition to raising awareness about the association of pterygia and the sport of surfing.

Linfante, I., Starosciak, A. K., Walker, G. R., Dabus, G., Castonguay, A. C., Gupta, R., et al. (2016).

Predictors of poor outcome despite recanalization: A multiple regression analysis of the NASA registry. *Journal of NeuroInterventional Surgery*, 8(3), 224-229.

Background Mechanical thrombectomy with stent retrievers results in higher recanalization rates compared with previous devices. Despite successful recanalization rates (Thrombolysis in Cerebral Infarction (TICI) score $\geq 2b$) of 70-83%, good outcomes by 90-day modified Rankin Scale (MRS) score ≤ 2 are achieved in only 40-55% of patients. We evaluated predictors of poor outcomes (MRS >2) despite successful recanalization (TICI $\geq 2b$) in the North American Solitaire Stent Retriever Acute Stroke (NASA) registry. Methods Logistic regression was used to evaluate baseline characteristics and recanalization outcomes for association with 90-day MRS score of 0-2 (good outcome) vs 3-6 (poor outcome). Univariate tests were carried out for all factors. A multivariable model was developed based on backwards selection from the factors with at least marginal significance ($p \leq 0.10$) on univariate analysis with the retention criterion set at $p \leq 0.05$. The model was refit to minimize the number of cases excluded because of missing covariate values; the c-statistic was a measure of predictive power. Results Of 354 patients, 256 (72.3%) were recanalized successfully. Based on 234 recanalized patients evaluated for 90-day MRS score, 116 (49.6%) had poor outcomes. Univariate analysis identified an increased risk of poor outcome for age ≥ 80 years, occlusion site of internal carotid artery (ICA)/basilar artery, National Institute of Health Stroke Scale (NIHSS) score ≥ 18 , history of diabetes mellitus, TICI 2b, use of rescue therapy, not using a balloon-guided catheter or intravenous tissue plasminogen activator (IV t-PA), and >30 min to recanalization ($p \leq 0.05$). In multivariable analysis, age ≥ 80 years, occlusion site ICA/basilar, initial NIHSS score ≥ 18 , diabetes, absence of IV t-PA, ≥ 3 passes, and use of rescue therapy were significant independent predictors of poor 90-day outcome in a model with good predictive power (c-index=0.80). Conclusions Age, occlusion site, high NIHSS, diabetes, no IV t-PA, ≥ 3 passes, and use of rescue therapy are associated with poor 90-day outcome despite successful recanalization.

Ling, W., Hillhouse, M. P., Saxon, A. J., Mooney, L. J., Thomas, C. M., Ang, A., et al. (2016).

Buprenorphine + naloxone plus naltrexone for the treatment of cocaine dependence: The cocaine use reduction with buprenorphine (CURB) study. *Addiction (Abingdon, England)*,

AIMS: To examine the safety and effectiveness of buprenorphine + naloxone sublingual tablets (BUP, as Suboxone(R)) provided after administration of extended-release injectable naltrexone (XR-NTX, as Vivitrol(R)) to reduce cocaine use in participants who met DSM-IV criteria for cocaine dependence and past or current opioid dependence or abuse. METHODS: This multi-

centered, double-blind, placebo-controlled study, conducted under the auspices of the National Drug Abuse Treatment Clinical Trials Network, randomly assigned 302 participants at sites in California, Oregon, Washington, Colorado, Texas, Georgia, Ohio, New York, and Washington D.C., USA to 1 of 3 conditions provided with XR-NTX: 4 mg/day BUP (BUP4, n = 100), 16 mg/day BUP (BUP16, n = 100), or no buprenorphine (placebo; PLB, n = 102). Participants received pharmacotherapy for 8 weeks, with 3 clinic visits per week. Cognitive Behavioral Therapy was provided weekly. Follow-up assessments occurred at 1 and 3 months post-intervention. The planned primary outcome was urine drug screen (UDS)-corrected, self-reported cocaine use during the last 4 weeks of treatment. Planned secondary analyses assessed cocaine use by UDS, medication adherence, retention, and adverse events. RESULTS: No group differences were found between groups for the primary outcome (BUP4 vs. PLB, $p = 0.262$; BUP16 vs PLB, $p = 0.185$).

Longitudinal analysis of UDS data during the evaluation period using generalized linear mixed equations found a statistically significant difference between BUP16 and PLB ($p = 0.022$, OR = 1.71) but not for BUP4 ($p = 0.105$, OR = 1.05). No secondary outcome differences across groups were found for adherence, retention, or adverse events. CONCLUSIONS: Buprenorphine + naloxone, used in combination with naltrexone, may be associated with reductions in cocaine use among people who meet DSM-IV criteria for cocaine dependence and past or current opioid dependence or abuse. This article is protected by copyright. All rights reserved.

Loudin, M., Childers, R., Zivony, A., Lanciault, C., Chang, M., & Ahn, J. (2016). Liver failure secondary to amyloid light-chain amyloidosis. *American Journal of Medicine*,

Lu, H. -, & Trussell, L. O. (2016). Spontaneous activity defines effective convergence ratios in an inhibitory circuit. *Journal of Neuroscience*, 36(11), 3268-3280.

Many neurons fire spontaneously, and the rate of this firing is subject to neuromodulation. How this firing affects functional connectivity within a neural network remains largely unexplored. Here we show that changes in spontaneous firing of cartwheel interneurons in the mouse dorsal cochlear nucleus (DCN) alter the effective convergence ratio of interneurons onto their postsynaptic targets through short-term synaptic plasticity. Spontaneous firing of cartwheel cells led to activity-dependent synaptic depression of individual cartwheel synapses. Depression was rapid and profound at stimulation frequencies between 10 and 200 Hz, suggesting the presence of high release probability (Pr) vesicles at these inhibitory synapses. Weak, transient synaptic facilitation could be induced after synapses were predepressed, indicating that low-Pr vesicles are also recruited, and may thus support steady-state transmission. A two-pool vesicle depletion model with 10-fold differences in Pr could account for the synaptic depression over a wide range of stimulus conditions. As a result of depression during high spontaneous activity, more cartwheel interneurons were required for effective inhibition. Convergence of four interneurons was sufficient to compensate for the effects of depression during physiologically expected rates of activity. By simulating synaptic release during spontaneous firing, we found that recruitment of low-Pr vesicles at the synapse plays a critical role in maintaining effective inhibition within a small population of interneurons. The interplay between spontaneous spiking, short-term synaptic plasticity, and vesicle recruitment thus determines the effective size of a convergent neural network. © 2016 the authors.

Luine, V. N., & Gomez, J. L. (2015). Sex differences in rodent cognitive processing and responses to chronic stress. (pp. 365-384) Elsevier Inc.

Chronic stress is associated with a different pattern of physiological, neural, and behavioral changes depending on the sex of the subject receiving the stress. In this review, the sex-dependent effects of chronic stress on learning and memory are reviewed in adult and developing (perinatal and adolescent) rodents. While males show impairments in aspects of cognitive function following chronic stress, females show a general resilience in performance of the same cognitive tasks following the same stresses. Moreover, studies show that alcohol alleviates stress-

dependent cognitive impairments in males but is associated with impaired cognition when it is administered to stressed females. The possible role of different learning and memory strategies in the sexes on the outcomes of chronic stress as well as the ability of estradiol to confer cognitive resilience to stress in females is discussed. Finally, the results presented are considered within the context of well described sex differences in mental disorders associated with stress and in relation to substance use/abuse. © 2016 Elsevier Inc. All rights reserved.

Lunsford, R., & Heeman, P. A. (2015). Using linguistic indicators of difficulty to identify mild cognitive impairment. *16th Annual Conference of the International Speech Communication Association, INTERSPEECH 2015, , 2015-January*. pp. 658-662.

Speaking is a complex task, and it is to be expected that speech will be effected when a speaker is faced with cognitive difficulties. To explore how cognitive impairment is manifested in a persons' speech, we compared the speech of elders diagnosed with Mild Cognitive Impairment (MCI) to others who are cognitively intact, while the speakers attempt to retell a story they just heard. We found that the speakers with impairment, as compared to those who are cognitively intact, spent more time engaged in verbalized hesitations (e.g., "and um ...") prior to speaking story content, and that these verbalized hesitations accounted for a larger ratio of the time spent retelling. In addition, we found that a higher percentage of the impaired speakers used phrases such as "I guess" and "I can't recall" to qualify content they were unsure of, or to replace details they couldn't recall. These results provide insight into how speakers manage cognitive impairment, suggesting that these indicators of difficulty could be used to assist in early diagnosis of MCI. Copyright © 2015 ISCA.

Lycette, J. (2016). Practicing hope. *JAMA Oncology*,

Mahapatra, S., & Scottoline, B. (2016). Steroid-induced resolution of refractory pulmonary interstitial emphysema. *The Journal of Maternal-Fetal & Neonatal Medicine : The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, , 1-4*.

Pulmonary interstitial emphysema (PIE) is a familiar complication of mechanical ventilation in premature infants. Its most severe form, marked by life-threatening respiratory and

cardiovascular compromise, is a particularly vexing problem in neonatology. Treatment modalities rely on decubitus positioning and reduction of mean airway pressure, but refractory PIE is unresponsive to these maneuvers. Other options such as selective unilateral bronchial intubation, balloon catheter bronchial occlusion, selective lung volume reduction, and mechanical decompression each have clear limitations. In a patient with refractory, life-threatening PIE too unstable for other therapeutic modalities, we describe success with steroid therapy at a familiar dosing regimen.

Mancini, M., Schlueter, H., El-Gohary, M., Mattek, N., Duncan, C., Kaye, J., et al. (2016). Continuous monitoring of turning mobility and its association to falls and cognitive function: A pilot study. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*,

BACKGROUND: Difficulty turning is a major contributor to mobility disability, falls, and reduced quality of life in older people because it requires dynamic balance control that worsens with age. However, no study has quantified the quality and quantity of turning during normal daily activities in older people. The objective of this pilot study was to determine if quality of turning during daily activities is associated with falls and/or cognitive function. METHODS: Thirty-five elderly participants (85+/-8 years) wore three Opal inertial sensors. Turning and activity rate were measured. Based on retrospective falls, participants were grouped into nonfallers (N = 16), single fallers (N = 12), and recurrent fallers (N = 7). We also determined which turning characteristic predicted falls in the 6 months following the week of monitoring. RESULTS: Quality of turning was significantly compromised in recurrent fallers compared with nonfallers ($p < .05$). In contrast, activity rate and mean number of turns per hour were similar across the three groups. Also, quality of turning during a prescribed test was similar across the three groups. Visuospatial and memory functions and the Tinetti Balance Scores were associated with quality of turning. Future falls were related to an increased variability of number of steps to turn.

CONCLUSIONS: Continuous monitoring of turning characteristics, while walking during daily activities, is feasible in older people. Turning characteristics during daily life appear to be more sensitive to fall risk than prescribed turning tasks. These findings suggest a slower, less variable, cautious turning strategy in elderly volunteers with a history of falls.

Manuck, T. A., Rice, M. M., Bailit, J. L., Grobman, W. A., Reddy, U. M., Wapner, R. J., et al. (2016).

Preterm neonatal morbidity and mortality by gestational age: A contemporary cohort. *American Journal of Obstetrics and Gynecology*,

Background: Although preterm birth 32 weeks. After 25 weeks, neonatal length of hospital stay decreased significantly with each additional completed week of pregnancy; among babies delivered from 26-32 weeks of gestation, each additional week in utero reduced the subsequent length of neonatal hospitalization by a minimum of 8 days. The median postmenstrual age at discharge nadired around 36 weeks' postmenstrual age for babies born at 31-35 weeks of gestation. Conclusion: Our data show that there is a continuum of outcomes, with each additional week of gestation conferring survival benefit while reducing the length of initial hospitalization. These contemporary data can be useful for patient counseling regarding preterm outcomes. Â© 2016 Elsevier Inc.

Marin, M., Golem, S., Kozak, S. L., & Kabat, D. (2016). Movements of HIV-1 genomic RNA-APOBEC3F complexes and PKR reveal cytoplasmic and nuclear PKR defenses and HIV-1 evasion strategies. *Virus Research*, 213, 124-139.

APOBEC3 cytidine deaminases and viral genomic RNA (gRNA) occur in virions, polysomes, and cytoplasmic granules, but have not been tracked together. Moreover, gRNA traffic is important, but the factors that move it into granules are unknown. Using in situ hybridization of transfected cells and protein synthesis inhibitors that drive mRNAs between locales, we observed APOBEC3F cotrafficking with gRNA without altering its movements. Whereas cells with little cytoplasmic gRNA were translationally active and accumulated Gag, suprathreshold amounts induced autophosphorylation of the cytoplasmic double-stranded RNA (dsRNA)-dependent protein kinase (PKR), causing eIF2 α phosphorylation, protein synthesis suppression, and gRNA sequestration in stress granules. Additionally, we confirmed recent evidence that PKR is activated by chromosome-associated cellular dsRNAs after nuclear membranes disperse in prophase. By arresting cells in G2, HIV-1 blocks this mechanism for PKR activation and eIF2 α phosphorylation. However, cytopathic membrane damage in CD4- and coreceptor-positive cultures infected with laboratory-adapted fusogenic HIV-1LAI eventually enabled PKR entry and activation in interphase nuclei. These results reveal multiple stages in the PKR-HIV-1 battleground that culminate in cell

death. We discuss evidence suggesting that HIV-1s evolve in vivo to prevent or delay PKR activation by all these mechanisms. © 2015 Elsevier B.V.

Marino, M., Bailey, S. R., Gold, R., Hoopes, M. J., O'Malley, J. P., Huguet, N., et al. (2016). Receipt of preventive services after Oregon's randomized medicaid experiment. *American Journal of Preventive Medicine*, 50(2), 161-170.

Introduction It is predicted that gaining health insurance via the Affordable Care Act will result in increased rates of preventive health services receipt in the U.S., primarily based on self-reported findings from previous health insurance expansion studies. This study examined the long-term (36-month) impact of Oregon's 2008 randomized Medicaid expansion ("Oregon Experiment") on receipt of 12 preventive care services in community health centers using electronic health record data. **Methods** Demographic data from adult (aged 19-64 years) Oregon Experiment participants were probabilistically matched to electronic health record data from 49 Oregon community health centers within the OCHIN community health information network (N=10,643). Intent-to-treat analyses compared receipt of preventive services over a 36-month (2008-2011) period among those randomly assigned to apply for Medicaid versus not assigned, and instrumental variable analyses estimated the effect of actually gaining Medicaid coverage on preventive services receipt (data collected in 2012-2014; analysis performed in 2014-2015). **Results** Intent-to-treat analyses revealed statistically significant differences between patients randomly assigned to apply for Medicaid (versus not assigned) for 8 of 12 assessed preventive services. In intent-to-treat analyses, Medicaid coverage significantly increased the odds of receipt of most preventive services (ORs ranging from 1.04 95% CI=1.02, 1.06] for smoking assessment to 1.27 95% CI=1.02, 1.57] for mammography). **Conclusions** Rates of preventive services receipt will likely increase as community health center patients gain insurance through Affordable Care Act expansions. Continued effort is needed to increase health insurance coverage in an effort to decrease health disparities in vulnerable populations. © 2016 American Journal of Preventive Medicine.

Martin, T. M. (2016). Familial uveitis. (pp. 673-680) Springer Berlin Heidelberg.

Familial uveitis is a term that when used broadly indicates the existence of uveitis within a family.

However, the presence of familial uveitis in a patient is not always informative with respect to diagnosis or predicting outcomes, and conversely, a particular uveitic diagnosis (with few exceptions) cannot predict the presence of uveitis in other family members. While some rare forms of uveitis clearly have a predominant genetic component, in most observations of familial uveitis, it is difficult, if not impossible on a case-by-case basis, to sort out the specific contributions of genetic factors versus environmental influences. © Springer-Verlag Berlin Heidelberg 2016.

Marzi, A., Murphy, A. A., Feldmann, F., Parkins, C. J., Haddock, E., Hanley, P. W., et al. (2016).

Cytomegalovirus-based vaccine expressing ebola virus glycoprotein protects nonhuman primates from ebola virus infection. *Scientific Reports*, 6

Ebolaviruses pose significant public health problems due to their high lethality, unpredictable emergence, and localization to the poorest areas of the world. In addition to implementation of standard public health control procedures, a number of experimental human vaccines are being explored as a further means for outbreak control. Recombinant cytomegalovirus (CMV)-based vectors are a novel vaccine platform that have been shown to induce substantial levels of durable, but primarily T-cell-biased responses against the encoded heterologous target antigen. Herein, we demonstrate the ability of rhesus CMV (RhCMV) expressing Ebola virus (EBOV) glycoprotein (GP) to provide protective immunity to rhesus macaques against lethal EBOV challenge. Surprisingly, vaccination was associated with high levels of GP-specific antibodies, but with no detectable GP-directed cellular immunity. © 2016, Nature Publishing Group. All rights reserved.

Masterson Creber, R., Patey, M., Lee, C. S., Kuan, A., Jurgens, C., & Riegel, B. (2016). Motivational interviewing to improve self-care for patients with chronic heart failure: MITI-HF randomized controlled trial. *Patient Education and Counseling*, 99(2), 256-264.

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.

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Matsumura, H., Chakraborty, S., Reed, J., Lu, Y., & Moenne-Loccoz, P. (2016). Effect of outer-sphere side chain substitutions on the fate of the trans iron-nitrosyl dimer in Heme/Nonheme engineered myoglobins (FeMbs): Insights into the mechanism of denitrifying NO reductases. *Biochemistry*, Denitrifying NO reductases are transmembrane protein complexes that utilize a heme/nonheme diiron center at their active sites to reduce two NO molecules to the innocuous gas N₂O. FeBMb proteins, with their nonheme iron sites engineered into the heme distal pocket of sperm whale myoglobin, are attractive models for studying the molecular details of the NO reduction reaction. Spectroscopic and structural studies of FeBMb constructs have confirmed that they reproduce the metal coordination spheres observed at the active site of the cytochrome c-dependent NO reductase from *Pseudomonas aeruginosa*. Exposure of FeBMb to excess NO, as examined by analytical and spectroscopic techniques, results primarily in the formation of a five-coordinate heme-nitrosyl complex without N₂O production. However, substitution of the outer-sphere residue Ile107 with a glutamic acid (i.e., I107E) decreases the formation rate of the five-coordinate heme-nitrosyl complex and allows for the substoichiometric production of N₂O. Here, we aim to better characterize the formation of the five-coordinate heme-nitrosyl complex and to explain why the level of N₂O production increases with the I107E substitution. We follow the formation of the five-coordinate heme-nitrosyl inhibitory complex through the sequential exposure of FeBMb to different NO isotopomers using rapid-freeze-quench resonance Raman spectroscopy. The data show that the complex is formed by the displacement of the proximal

histidine by a new NO molecule after the weakening of the Fe(II)-His bond in the intermediate six-coordinate low-spin (6cLS) heme-nitrosyl complex. These results lead us to explore diatomic migration within the scaffold of myoglobin and whether substitutions at residue 107 can be sufficient to control access to the proximal heme cavities. Results on a new FeBmb construct with an I107F substitution (FeBmb3) show an increased rate for the formation of the five-coordinate low-spin heme-nitrosyl complex without N₂O production. Taken together, our results suggest that production of N₂O from the [6cLS heme {FeNO}7/{FeBNO}7] trans iron-nitrosyl dimer intermediate requires a proton transfer event facilitated by an outer-sphere residue such as E107 in FeBmb2 and E280 in *P. aeruginosa* cNOR.

Maxson, J. E., Abel, M. L., Wang, J., Deng, X., Reckel, S., Luty, S. B., et al. (2016). Identification and characterization of tyrosine kinase nonreceptor 2 mutations in leukemia through integration of kinase inhibitor screening and genomic analysis. *Cancer Research*, 76(1), 127-138.

The amount of genomic information about leukemia cells currently far exceeds our overall understanding of the precise genetic events that ultimately drive disease development and progression. Effective implementation of personalized medicine will require tools to distinguish actionable genetic alterations within the complex genetic landscape of leukemia. In this study, we performed kinase inhibitor screens to predict functional gene targets in primary specimens from patients with acute myeloid leukemia and chronic myelomonocytic leukemia. Deep sequencing of the same patient specimens identified genetic alterations that were then integrated with the functionally important targets using the HitWalker algorithm to prioritize the mutant genes that most likely explain the observed drug sensitivity patterns. Through this process, we identified tyrosine kinase nonreceptor 2 (TNK2) point mutations that exhibited oncogenic capacity. Importantly, the integration of functional and genomic data using HitWalker allowed for prioritization of rare oncogenic mutations that may have been missed through genomic analysis alone. These mutations were sensitive to the multikinase inhibitor dasatinib, which antagonizes TNK2 kinase activity, as well as novel TNK2 inhibitors, XMD8-87 and XMD16-5, with greater target specificity. We also identified activating truncation mutations in other tumor types that were sensitive to XMD8-87 and XMD16-5, exemplifying the potential utility of these compounds across tumor types dependent on TNK2. Collectively, our findings highlight a more sensitive

approach for identifying actionable genomic lesions that may be infrequently mutated or overlooked and provide a new method for the prioritization of candidate genetic mutations. © 2015 American Association for Cancer Research.

Maxson, J. E., Luty, S. B., MacManiman, J. D., Paik, J. C., Gotlib, J., Greenberg, P., et al. (2016). The colony-stimulating factor 3 receptor T640N mutation is oncogenic, sensitive to JAK inhibition, and mimics T618I. *Clinical Cancer Research*, 22(3), 757-764.

Purpose: Colony-stimulating factor 3 receptor (CSF3R) mutations have been identified in the majority of chronic neutrophilic leukemia (CNL) and a smaller percentage of atypical chronic myeloid leukemia (aCML) cases. Although CSF3R point mutations (e.g., T618I) are emerging as key players in CNL/aCML, the significance of rarer CSF3R mutations is unknown. In this study, we assess the importance of the CSF3R T640N mutation as a marker of CNL/aCML and potential therapeutic target. Experimental Design: Sanger sequencing of leukemia samples was performed to identify CSF3R mutations in CNL and aCML. The oncogenicity of the CSF3R T640N mutation relative to the T618I mutation was assessed by cytokine independent growth assays and by mouse bone marrow transplant. Receptor dimerization and O-glycosylation of the mutants was assessed by Western blot, and JAK inhibitor sensitivity was assessed by colony assay. Results: Here, we identify a CSF3R T640N mutation in two patients with CNL/aCML, one of whom was originally diagnosed with MDS and acquired the T640N mutation upon evolution of disease to aCML. The T640N mutation is oncogenic in cellular transformation assays and an in vivo mouse bone marrow transplantation model. It exhibits many similar phenotypic features to T618I, including ligand independence and altered patterns of O-glycosylation—despite the transmembrane location of T640 preventing access by GalNAc transferase enzymes. Cells transformed by the T640N mutation are sensitive to JAK kinase inhibition to a similar degree as cells transformed by CSF3R T618I. Conclusions: Because of its similarities to CSF3R T618I, the T640N mutation likely has diagnostic and therapeutic relevance in CNL/aCML. ©2015 AACR.

McAllister, M., Levett-Jones, T., Petrini, M. A., & Lasater, K. (2016). The viewing room: A lens for developing ethical comportment. *Nurse Education in Practice*, 16(1), 119-124.

Healthcare is dynamic and complex, and against this background, nursing students must

negotiate the transition from lay person to healthcare professional. Diverse life experiences and learning styles can further complicate this journey of transformation. The contemporary role of the nurse includes caring for and making clinical decisions about patients based on ethical principles. Learning about and integrating ethical comportment as part of the transformative journey requires nurse educators to create and implement learning experiences that challenge nursing students to think deeply and broadly about the experiences they encounter, to question their previous assumptions and prejudices, to consider the world of healthcare through a new lens, and to reflect on and learn from the process. The judicious use of film has the potential to assist students to recognize and develop ethical comportment as they prepare for real-world clinical practice experiences. In this paper, we present three film exemplars and related teaching strategies designed to facilitate transformative learning and development of ethical comportment.

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McCammond, A. N., Axelrod, D. M., Bailly, D. K., Ramsey, E. Z., & Costello, J. M. (2016). Pediatric cardiac intensive care society 2014 consensus statement: Pharmacotherapies in cardiac critical care fluid management. *Pediatric Critical Care Medicine : A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*, 17(3 Suppl 1), S35-48.

OBJECTIVE: In this Consensus Statement, we review the etiology and pathophysiology of fluid disturbances in critically ill children with cardiac disease. Clinical tools used to recognize pathologic fluid states are summarized, as are the mechanisms of action of many drugs aimed at optimal fluid management. **DATA SOURCES:** The expertise of the authors and a review of the medical literature were used as data sources. **DATA SYNTHESIS:** The authors synthesized the data in the literature in order to present clinical tools used to recognize pathologic fluid states. For each drug, the physiologic rationale, mechanism of action, and pharmacokinetics are synthesized, and the evidence in the literature to support the therapy is discussed.

CONCLUSIONS: Fluid management is challenging in critically ill pediatric cardiac patients. A myriad of causes may be contributory, including intrinsic myocardial dysfunction with its associated neuroendocrine response, renal dysfunction with oliguria, and systemic inflammation with resulting endothelial dysfunction. The development of fluid overload has been associated

with adverse outcomes, including acute kidney injury, prolonged mechanical ventilation, increased vasoactive support, prolonged hospital length of stay, and mortality. An in-depth understanding of the many factors that influence volume status is necessary to guide optimal management.

McCarty, O. J., Ku, D., Sugimoto, M., King, M. R., Cosemans, J. M., Neeves, K. B., et al. (2016).

Dimensional analysis and scaling relevant to flow models of thrombus formation: Communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis : JTH*, 14(3), 619-622.

McClave, S. A., DiBaise, J. K., Mullin, G. E., & Martindale, R. G. (2016). ACG clinical guideline:

Nutrition therapy in the adult hospitalized patient. *The American Journal of Gastroenterology*, 111(3), 315-334.

The value of nutrition therapy for the adult hospitalized patient is derived from the outcome benefits achieved by the delivery of early enteral feeding. Nutritional assessment should identify those patients at high nutritional risk, determined by both disease severity and nutritional status. For such patients if they are unable to maintain volitional intake, enteral access should be attained and enteral nutrition (EN) initiated within 24-48 h of admission. Orogastric or nasogastric feeding is most appropriate when starting EN, switching to post-pyloric or deep jejunal feeding only in those patients who are intolerant of gastric feeds or at high risk for aspiration. Percutaneous access should be used for those patients anticipated to require EN for >4 weeks. Patients receiving EN should be monitored for risk of aspiration, tolerance, and adequacy of feeding (determined by percent of goal calories and protein delivered). Intentional permissive underfeeding (and even trophic feeding) is appropriate temporarily for certain subsets of hospitalized patients. Although a standard polymeric formula should be used routinely in most patients, an immune-modulating formula (with arginine and fish oil) should be reserved for patients who have had major surgery in a surgical ICU setting. Adequacy of nutrition therapy is enhanced by establishing nurse-driven enteral feeding protocols, increasing delivery by volume-based or top-down feeding strategies, minimizing interruptions, and eliminating the practice of gastric residual volumes. Parenteral nutrition should be used in patients at high nutritional risk when EN is not feasible or after the first week of hospitalization if EN is not sufficient. Because of

their knowledge base and skill set, the gastroenterologist endoscopist is an asset to the Nutrition Support Team and should participate in providing optimal nutrition therapy to the hospitalized adult patient.

McConnell, K. J., Lindrooth, R. C., Wholey, D. R., Maddox, T. M., & Bloom, N. (2016). Modern management practices and hospital admissions. *Health Economics (United Kingdom)*, 25(4), 470-485.

We investigate whether the modern management practices and publicly reported performance measures are associated with choice of hospital for patients with acute myocardial infarction (AMI). We define and measure management practices at approximately half of US cardiac care units using a novel survey approach. A patient's choice of a hospital is modeled as a function of the hospital's performance on publicly reported quality measures and the quality of its management. The estimates, based on a grouped conditional logit specification, reveal that higher management scores and better performance on publicly reported quality measures are positively associated with hospital choice. Management practices appear to have a direct correlation with admissions for AMI - potentially through reputational effects - and indirect association, through better performance on publicly reported measures. Overall, a one standard deviation change in management practice scores is associated with an 8% increase in AMI admissions. Copyright © 2015 John Wiley & Sons, Ltd.

McGill, T. J., Renner, L. M., & Neuringer, M. (2016). Elevated fundus autofluorescence in monkeys deficient in lutein, zeaxanthin, and omega-3 fatty acids. *Investigative Ophthalmology & Visual Science*, 57(3), 1361-1369.

PURPOSE: We quantified fundus autofluorescence (FAF) in the nonhuman primate retina as a function of age and diets lacking lutein and zeaxanthin (L/Z) and omega-3 fatty acids. METHODS: Quantitative FAF was measured in a cross-sectional study of rhesus macaques fed a standard diet across the lifespan, and in aged rhesus macaques fed lifelong diets lacking L/Z and providing either adequate or deficient levels of omega-3 fatty acids. Macular FAF images were segmented into multiple regions of interest, and mean gray values for each region were calculated using ImageJ. The resulting FAF values were compared across ages within the standard diet animals,

and among diet groups and regions. RESULTS: Fundus autofluorescence increased with age in the standard diet animals, and was highest in the perifovea. Monkeys fed L/Z-free diets with either adequate or deficient omega-3 fatty acids had significantly higher FAF overall than age-matched standard diet monkeys. Examined by region, those with adequate omega-3 fatty acids had higher FAF in the fovea and superior regions, while monkeys fed the diet lacking L/Z and omega-3 fatty acids had higher FAF in all regions. CONCLUSIONS: Diets devoid of L/Z resulted in increased retinal autofluorescence, with the highest values in animals also lacking omega-3 fatty acids. The increase was equivalent to a 12- to 20-year acceleration in lipofuscin accumulation compared to animals fed a standard diet. Together these data add support for the role of these nutrients as important factors in lipofuscin accumulation, retinal aging, and progression of macular disease.

Mcginley, K. F., Sun, X., Howard, L. E., Aronson, W. J., Terris, M. K., Kane, C. J., et al. (2016).

Utilization and impact of surgical technique on the performance of pelvic lymph node dissection at radical prostatectomy: Results from the shared equal access regional cancer hospital database.

International Journal of Urology, 23(3), 241-246.

Objective: To evaluate performance of pelvic lymph node dissection during radical prostatectomy within an equal access care setting over a period of time, and stratified by prostate cancer risk group and surgical technique. Methods: We identified men in the Shared Equal Access Regional Cancer Hospital database who had open or robotic-assisted radical prostatectomy from 2006 to 2013. Univariable logistic regression was used to test the association between age, race, body mass index, total biopsy cores, number of positive biopsy cores, risk group, year, center, surgical volume and surgical technique on pelvic lymph node dissection use. Multivariable logistic analysis was used to examine surgical technique and pelvic lymph node dissection performance.

Spearman's correlation examined temporal changes in pelvic lymph node dissection utilization stratified by risk group and surgical technique. Results: A total of 1425 men met inclusion criteria; 67% of them underwent pelvic lymph node dissection. On multivariable analysis, robotic-assisted radical prostatectomy was associated with an 92% decreased use of pelvic lymph node dissection in low-risk, 84% decreased in intermediate-risk and 91% decreased in high-risk men (all $P < 0.001$). In robotic-assisted radical prostatectomy, there was a trend for increased pelvic

lymph node dissection utilization over time in high-risk men (Spearman; $P = 0.077$) reaching ~85% in 2012-2013, which was accompanied by increased use in low-risk men ($P = 0.016$). For open radical prostatectomy, fewer pelvic lymph node dissections were carried out in low-risk men over time, decreasing to ~35% ($P = 0.047$) in 2012-2013, whereas rates remained high for high-risk men throughout (~95%; $P = 0.621$). Conclusion: Regardless of risk group, pelvic lymph node dissection is carried out significantly less during robotic-assisted radical prostatectomy. For robotic-assisted radical prostatectomy, pelvic lymph node dissection utilization increased over time for high-risk men, but rates also increased for low-risk men. Further attention to the discrepancy between provided and guideline recommended pelvic lymph node dissection performance is required to improve prostate cancer care. © 2016 The Japanese Urological Association.

McKenzie, G., Freiheit, H., Steers, D., & Noone, J. (2016). Veteran and family health: Building competency with unfolding cases. *Clinical Simulation in Nursing, 12*(3), 79-83.

There are 22 million veterans in the United States and more than one million children who have a parent deployed in the military. As the number of veterans in need of health services increases, it is imperative for nurses in all care settings to understand the potential impact of military service on the veteran and their families. This article introduces an innovative set of unfolding live-actor cases used in classroom and simulation for students to gain competency in caring for veterans and their families. Adaptation of existing learning activities is one way to infuse veteran-related concepts into a program of study. © 2016 International Nursing Association for Clinical Simulation and Learning.

Mcmullen, C., Wilfond, B. S., Lynch, F. L., Reiss, J. A., Gilmore, M. J., Himes, P., et al. (2016).

Patients' ratings of genetic conditions validate a taxonomy to simplify decisions about preconception carrier screening via genome sequencing. *American Journal of Medical Genetics, Part A, 170*(3), 574-582.

Advances in genome sequencing and gene discovery have created opportunities to efficiently assess more genetic conditions than ever before. Given the large number of conditions that can be screened, the implementation of expanded carrier screening using genome sequencing will

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

McQuilken, A. C., Matsumura, H., Durr, M., Confer, A. M., Sheckelton, J. P., Siegler, M. A., et al. (2016). Photoinitiated reactivity of a thiolate-ligated, spin-crossover nonheme $\{FeNO\}(7)$ complex with dioxygen. *Journal of the American Chemical Society*, *138*(9), 3107-3117.

The nonheme iron complex, $[Fe(NO)(N3PyS)]BF_4$, is a rare example of an $\{FeNO\}(7)$ species that exhibits spin-crossover behavior. The comparison of X-ray crystallographic studies at low and high temperatures and variable-temperature magnetic susceptibility measurements show that a low-spin $S = 1/2$ ground state is populated at 0-150 K, while both low-spin $S = 1/2$ and high-spin $S = 3/2$ states are populated at $T > 150$ K. These results explain the observation of two N-O vibrational modes at 1737 and 1649 cm^{-1} in CD_3CN for $[Fe(NO)(N3PyS)]BF_4$ at room temperature. This $\{FeNO\}(7)$ complex reacts with dioxygen upon photoirradiation with visible light in acetonitrile to generate a thiolate-ligated, nonheme iron(III)-nitro complex, $[Fe(III)(NO_2)(N3PyS)](+)$, which was characterized by EPR, FTIR, UV-vis, and CSI-MS. Isotope

labeling studies, coupled with FTIR and CSI-MS, show that one O atom from O₂ is incorporated in the Fe(III)-NO₂ product. The O₂ reactivity of [Fe(NO)(N₃PyS)]BF₄ in methanol is dramatically different from CH₃CN, leading exclusively to sulfur-based oxidation, as opposed to NO. oxidation. A mechanism is proposed for the NO. oxidation reaction that involves formation of both Fe(III)-superoxo and Fe(III)-peroxynitrite intermediates and takes into account the experimental observations. The stability of the Fe(III)-nitrite complex is limited, and decay of [Fe(III)(NO₂)(N₃PyS)](+) leads to {FeNO}(7) species and sulfur oxygenated products. This work demonstrates that a single mononuclear, thiolate-ligated nonheme {FeNO}(7) complex can exhibit reactivity related to both nitric oxide dioxygenase (NOD) and nitrite reductase (NiR) activity. The presence of the thiolate donor is critical to both pathways, and mechanistic insights into these biologically relevant processes are presented.

Meinel, S., Blohberger, J., Berg, D., Berg, U., Dissen, G. A., Ojeda, S. R., et al. (2015). Pro-nerve growth factor in the ovary and human granulosa cells. *Hormone Molecular Biology and Clinical Investigation*, 24(2), 91-99.

Background: Pro-nerve growth factor must be cleaved to generate mature NGF, which was suggested to be a factor involved in ovarian physiology and pathology. Extracellular proNGF can induce cell death in many tissues. Whether extracellular proNGF exists in the ovary and may play a role in the death of follicular cells or atresia was unknown. Materials and methods:

Immunohistochemistry of human and rhesus monkey ovarian sections was performed. IVF-derived follicular fluid and human granulosa cells were studied by RT-PCR, qPCR, Western blotting, ATP- and caspase-assays. Results and conclusion: Immunohistochemistry of ovarian sections identified proNGF in granulosa cells and Western blotting of human isolated granulosa cells confirmed the presence of proNGF. Ovarian granulosa cells thus produce proNGF.

Recombinant human proNGF even at high concentrations did not affect the levels of ATP or the activity of caspase 3/7, indicating that in granulosa cells proNGF does not induce death. In contrast, mature NGF, which was detected previously in follicular fluid, may be a trophic molecule for granulosa cells with unexpected functions. We found that in contrast to proNGF, NGF increased the levels of the transcription factor early growth response 1 and of the enzyme choline acetyl-transferase. A mechanism for the generation of mature NGF from proNGF in the follicular

fluid may be extracellular enzymatic cleavage. The enzyme MMP7 is known to cleave proNGF and was identified in follicular fluid and as a product of granulosa cells. Thus the generation of NGF in the ovarian follicle may depend on MMP7. © 2015 by De Gruyter 2015.

Mejía-Pérez, D., Ángel-Müller, E., Rodríguez-Hernández, A. E., Ruiz-Parra, A. I., Tolosa-Ardila, J. E., & Gaitán-Duarte, H. (2015). Operational characteristics of the clinical diagnosis in the office, with and without tests (pH and amine test), for diagnosing bacterial vaginosis in symptomatic patients in bogotá, colombia. [Características operativas del diagnóstico clínico con y sin pruebas de consultorio (pH y prueba de aminas) para el diagnóstico de vaginosis bacteriana, en pacientes sintomáticas en Bogotá, Colombia] *Revista Colombiana De Obstetricia y Ginecologia*, 66(4), 253-262.

Objective: To assess the operational characteristics of the clinical diagnosis (signs and symptoms) alone and with diagnostic tests in the office (pH and amine test), using the Nugent score as the gold standard for diagnosing bacterial vaginosis. Materials and methods: Diagnostic validity study assembled in a cross sectional study in patients with symptoms of lower genitourinary tract infection seen in 3 centres in Bogota in 2010. The calculated sample size was 1400 participants, and a sequential sampling was used. Samples were taken from the vaginal wall for pH measurement, amine test and Gram staining in order to derive the Nugent score, considered the gold standard in this disease. The lab technicians were blinded to the clinical diagnosis and to the office tests. Sensitivity, specificity ad odds ratio OR (+) and OR (-) were measured, and they are presented as proportions with their respective 95% confidence intervals. Results: The prevalence of bacterial vaginosis was 39.6 %, and the operational characteristics of the tests with their respective 95 % CI were as follows: sensitivity and specificity of the clinical diagnosis were 75 % (71-78) and 54 % (51-57), respectively; sensitivity and specificity of pH \geq 5 were 99.3 % (98.2-99.8), and 0.57 % (0.2-1.3); amine test sensitivity 99.3 % (98.2-99.8 %) and specificity 99.8 % (99.2-100 %); clinical diagnosis plus amine test and pH \geq 5.0, sensitivity 74 % (71- 78), specificity 100 % (99-100). Conclusions: Clinical diagnosis showed a good sensitivity for diagnosing strategy for diagnosing bacterial vaginosis; specificity is improved when clinical findings are combined with amine test and vaginal pH. The amine test was shown to have

excellent sensitivity and specificity, and it is useful to improve the diagnosis of bacterial vaginosis.

Messer, W. B., Yount, B. L., Royal, S. R., de Alwis, R., Widman, D. G., Smith, S. A., et al. (2016).

Functional transplant of a DENV3-specific human monoclonal antibody epitope into DENV1.

Journal of Virology,

The four dengue virus (DENV) serotypes, DENV1 through 4, are endemic throughout tropical and sub-tropical regions of the world. While first infection confers long-term protective immunity against viruses of the infecting serotype, second infection with virus of a different serotype carries a greater risk of severe dengue disease, including dengue hemorrhagic fever and dengue shock syndrome. Recent studies demonstrate that humans exposed to DENV infections develop neutralizing antibodies that bind to quaternary epitopes formed by the viral Envelope (E) protein dimers or higher order assemblies required for the formation of the icosahedral viral envelope. Here we show that the quaternary epitope target of the human DENV3-specific neutralizing monoclonal antibody (mAb), 5J7, can be partially transplanted into a DENV1 strain by changing the core residues of the epitope contained within a single monomeric E molecule. The mAb 5J7 neutralized the recombinant DENV1/3 strain in cell culture and was protective in a mouse model of infection with the DENV1/3 strain. However, the 5J7 epitope was only partially recreated by transplantation of the core residues because the 5J7 mAb bound and neutralized WT DENV3 better than the DENV1/3 recombinant. Our studies demonstrate that it is possible to transplant a large number of discontinuous residues between DENV serotypes and partially recreate a complex antibody epitope, while retaining virus viability. Further refinement of this approach may lead to new tools for measuring epitope-specific antibody responses and new vaccine platforms.

IMPORTANCE: Dengue virus is the most important mosquito-borne pathogen of humans worldwide, with approximately one-half the world's population living in dengue endemic regions. Dengue immunity following infection is robust and thought to be conferred by antibodies raised against the infecting virus. However, the specific viral components these antibodies recognize and how they neutralize the virus have been incompletely described. Here we map a region on dengue virus serotype 3 recognized by the human neutralizing antibody, 5J7, and then test the functional significance of this region by transplanting it into a serotype 1 virus. Our studies

demonstrate a region on dengue virus necessary for 5J7 binding and neutralization. Our work also demonstrates the technical feasibility of engineering dengue viruses to display targets of protective antibodies. This technology can be used to develop new dengue vaccines and diagnostic assays.

Mitrugno, A., Tormoen, G. W., Kuhn, P., & McCarty, O. J. T. (2016). The prothrombotic activity of cancer cells in the circulation. *Blood Reviews*, 30(1), 11-19.

The hemostatic system is often subverted in patients with cancer, resulting in life-threatening venous thrombotic events. Despite the multifactorial and complex etiology of cancer-associated thrombosis, changes in the expression and activity of cancer-derived tissue factor (TF) - the principle initiator of the coagulation cascade - are considered key to malignant hypercoagulopathy and to the pathophysiology of thrombosis. However, many of the molecular and cellular mechanisms coupling the hemostatic degeneration to malignancy remain largely uncharacterized. In this review we discuss some of the tumor-intrinsic and tumor-extrinsic mechanisms that may contribute to the prothrombotic state of cancer, and we bring into focus the potential for circulating tumor cells (CTCs) in advancing our understanding of the field. We also summarize the current status of anti-coagulant therapy for the treatment of thrombosis in patients with cancer. © 2015.

Mohammadi, S. H., & Kain, A. (2015). Semi-supervised training of a voice conversion mapping function using a joint-autoencoder. *16th Annual Conference of the International Speech Communication Association, INTERSPEECH 2015, , 2015-January*. pp. 284-288.

Recently, researchers have begun to investigate Deep Neural Network (DNN) architectures as mapping functions in voice conversion systems. In this study, we propose a novel Stacked-Joint-Autoencoder (SJAE) architecture, which aims to find a common encoding of parallel source and target features. The SJAE is initialized from a Stacked-Autoencoder (SAE) that has been trained on a large general-purpose speech database. We also propose to train the SJAE using unrelated speakers that are similar to the source and target speaker, instead of using only the source and target speakers. The final DNN is constructed from the source-encoding part and the target-decoding part of the SJAE, and then fine-tuned using back-propagation. The use of this semi-

supervised training approach allows us to use multiple frames during mapping, since we have previously learned the general structure of the acoustic space and also the general structure of similar source-target speaker mappings. We train two speaker conversions and compare several system configurations objectively and subjectively while varying the number of available training sentences. The results show that each of the individual contributions of SAE, SJAE, and using unrelated speakers to initialize the mapping function increases conversion performance.

Copyright © 2015 ISCA.

Montaño, A. M., Lock-Hock, N., Steiner, R. D., Graham, B. H., Szlago, M., Greenstein, R., et al.

(2016). Clinical course of sly syndrome (mucopolysaccharidosis type VII). *Journal of Medical Genetics*,

Background Mucopolysaccharidosis VII (MPS VII) is an ultra-rare disease characterised by the deficiency of β -glucuronidase (GUS). Patients' phenotypes vary from severe forms with hydrops fetalis, skeletal dysplasia and mental retardation to milder forms with fewer manifestations and mild skeletal abnormalities. Accurate assessments on the frequency and clinical characteristics of the disease have been scarce. The aim of this study was to collect such data. Methods We have conducted a survey of physicians to document the medical history of patients with MPS VII. The survey included anonymous information on patient demographics, family history, mode of diagnosis, age of onset, signs and symptoms, severity, management, clinical features and natural progression of the disease. Results We collected information on 56 patients from 11 countries. Patients with MPS VII were classified based on their phenotype into three different groups: (1) neonatal non-immune hydrops fetalis (NIHF) (n=10), (2) Infantile or adolescent form with history of hydrops fetalis (n=13) and (3) Infantile or adolescent form without known hydrops fetalis (n=33). Thirteen patients with MPS VII who had the infantile form with history of hydrops fetalis and survived childhood, had a wide range of clinical manifestations from mild to severe. Five patients underwent bone marrow transplantation and one patient underwent enzyme replacement therapy with recombinant human GUS. Conclusions MPS VII is a pan-ethnic inherited lysosomal storage disease with considerable phenotypical heterogeneity. Most patients have short stature, skeletal dysplasia, hepatosplenomegaly, hernias, cardiac involvement, pulmonary insufficiency and cognitive impairment. In these respects it resembles MPS I and MPS

II. In MPS VII, however, one unique and distinguishing clinical feature is the unexpectedly high proportion of patients (41%) that had a history of NIHF. Presence of NIHF does not, by itself, predict the eventual severity of the clinical course, if the patient survives infancy. © 2016 by the BMJ Publishing Group Ltd.

Mooney, M. A., McWeeney, S. K., Faraone, S., Hinney, A., Hebebrand, J., IMAGE2 Consortium, et al. (2016). Pathway analysis in attention deficit hyperactivity disorder: An ensemble approach. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*,

Despite a wealth of evidence for the role of genetics in attention deficit hyperactivity disorder (ADHD), specific and definitive genetic mechanisms have not been identified. Pathway analyses, a subset of gene-set analyses, extend the knowledge gained from genome-wide association studies (GWAS) by providing functional context for genetic associations. However, there are numerous methods for association testing of gene sets and no real consensus regarding the best approach. The present study applied six pathway analysis methods to identify pathways associated with ADHD in two GWAS datasets from the Psychiatric Genomics Consortium. Methods that utilize genotypes to model pathway-level effects identified more replicable pathway associations than methods using summary statistics. In addition, pathways implicated by more than one method were significantly more likely to replicate. A number of brain-relevant pathways, such as RhoA signaling, glycosaminoglycan biosynthesis, fibroblast growth factor receptor activity, and pathways containing potassium channel genes, were nominally significant by multiple methods in both datasets. These results support previous hypotheses about the role of regulation of neurotransmitter release, neurite outgrowth and axon guidance in contributing to the ADHD phenotype and suggest the value of cross-method convergence in evaluating pathway analysis results. (c) 2016 Wiley Periodicals, Inc.

Morasco, B. J., Peters, D., Krebs, E. E., Kovas, A. E., Hart, K., & Dobscha, S. K. (2016). Predictors of urine drug testing for patients with chronic pain: Results from a national cohort of U.S. veterans. *Substance Abuse*, 1-6.

Background: Urine drug testing (UDT) is recommended for all patients who initiate chronic opioid

therapy (COT) for the treatment of chronic pain; however, it is infrequently utilized. Some prior research has identified factors that may predict UDT, but studies have been limited. The purpose of this study is to examine the rate and predictors of UDT among a national sample of patients with chronic pain who had new initiations of COT. Methods: Administrative data were examined for all veterans receiving medical care at Department of Veterans Affairs medical facilities who had new initiations of chronic opioid therapy (COT) during fiscal year 2011. Results: Nineteen percent of patients who had new initiations of COT for chronic noncancer pain received UDT within 90 days of starting opioids. In adjusted analyses, patient-level factors that predicted increased likelihood of UDT included male gender (risk ratio [RR] = 1.23, 95% confidence interval [CI] = 1.02–1.49), Black race (RR = 1.20, 95% CI = 1.06–1.37), divorced/separated marital status (RR = 1.13, 95% CI = 1.02–1.25), higher pain intensity (RR = 1.03, 95% CI = 1.01–1.05), comorbid substance use disorder (RR = 1.42, 95% CI = 1.27–1.60), posttraumatic stress disorder (PTSD) (RR = 1.14, 95% CI = 1.01–1.29), bipolar disorder or schizophrenia (RR = 1.29, 95% CI = 1.08–1.53), having received UDT prior to initiating opioid therapy (RR = 1.43, 95% CI = 1.26–1.62), and a higher baseline opioid dose (RR = 1.38–1.81, 95% CIs = 1.20–1.58, 1.57–2.09). Age was also associated with UDT, in a nonlinear manner. Several factors were associated with lower likelihood of UDT, including living in a highly rural setting (RR = 0.62, 95% CI = 0.29–0.99), having a VA service-connected disability (RR = 0.85–0.89, 95% CIs = 0.75–0.97, 0.79–0.99), and having a nurse practitioner or physician assistant as one's primary care clinician (RR = 0.72, 95% CI = 0.61–0.85). Conclusions: Urine drug testing was conducted with 19% of patients who had new initiations of COT. Factors that predicted UDT were multifaceted and included patient and clinician variables. Multidimensional system-level interventions may be needed to facilitate widespread implementation of UDT. © 2016 Taylor & Francis Group, LLC

Morgan, T. K., Allen-Brady, K. L., Monson, M. A., Leclair, C. M., Sharp, H. T., & Cannon-Albright, L. A. (2016). Familiality analysis of provoked vestibulodynia treated by vestibulectomy supports genetic predisposition. *American Journal of Obstetrics and Gynecology*,
Background: Provoked vestibulodynia is a poorly understood disease that affects 8-15% of women in their lifetime. There is significant inflammation and nerve growth in vestibular biopsies

from affected women treated by vestibulectomy compared with matched female population controls without vestibulodynia. The triggers leading to this neurogenic inflammation are unknown, but they are likely multifactorial. Objective: Our objective was to determine whether vestibulodynia is more common in close and distantly related female relatives of women diagnosed with the disease and those specifically treated by vestibulectomy. Excess familial clustering would support a potential genetic predisposition for vestibulodynia and warrant further studies to isolate risk alleles. Study Design: Using population-based genealogy linked to University of Utah Hospital CPT coded data, we estimated the relative risk of vestibulectomy in female relatives of affected women. We also compared the average pairwise relatedness of cases to the expected relatedness of the population and identified high-disease-burden pedigrees. Results: A total of 183 potential vestibulectomy probands were identified using CPT codes. The relative risk of vestibulectomy was elevated in first-degree (20 [6.6-47], $P < .00001$), second-degree (4.5 [0.5-16], $P = .07$), and third-degree female relatives (3.4 [1.2-8.8], $P = .03$). Seventy of these 183 CPT-based probands had available clinical history to confirm a diagnosis of moderate to severe vestibulodynia. Notably, this smaller group of confirmed probands ($n = 70$) revealed a similar familiarity in first-degree (54 [17.5-126], $P < .00001$), second-degree (19.7 [2.4-71], $P = .005$), and third-degree relatives (12 [3.3-31], $P = .0004$), despite less statistical power for analysis. Overall, the average pairwise relatedness of affected women was significantly higher than expected ($P < .001$) and a number of high-disease-burden Utah families were identified. Conclusion: Our data suggest that vestibulodynia treated by vestibulectomy has a genetic predisposition. Future studies will identify candidate genes by linkage analysis in affected families and sequencing of distantly related probands. © 2016 Elsevier Inc.

Morrison, J. J., Hostetter, J. M., Aggarwal, A., & Filice, R. W. (2016). Constructing a computer-aided differential diagnosis engine from open-source APIs. *Journal of Digital Imaging*,

This paper describes the design and implementation of an application that parses and analyzes radiology report text to provide a radiologic differential diagnosis. The system was constructed using a combination of freely available web-based APIs and originally developed during the Society for Imaging Informatics in Medicine (SIIM) 2014 Hackathon. Continued development has refined and increased the accuracy of the algorithm. This project demonstrates the power and

possibilities of combining existing technologies to solve unique problems as well as the stimulus of the hackathon setting to spur innovation.

Morrison, S. F. (2016). Central neural control of thermoregulation and brown adipose tissue.

Autonomic Neuroscience : Basic & Clinical,

Central neural circuits orchestrate the homeostatic repertoire that maintains body temperature during environmental temperature challenges and alters body temperature during the inflammatory response. This review summarizes the experimental underpinnings of our current model of the CNS pathways controlling the principal thermoeffectors for body temperature regulation: cutaneous vasoconstriction controlling heat loss, and shivering and brown adipose tissue for thermogenesis. The activation of these effectors is regulated by parallel but distinct, effector-specific, core efferent pathways within the CNS that share a common peripheral thermal sensory input. Via the lateral parabrachial nucleus, skin thermal afferent input reaches the hypothalamic preoptic area to inhibit warm-sensitive, inhibitory output neurons which control heat production by inhibiting thermogenesis-promoting neurons in the dorsomedial hypothalamus that project to thermogenesis-controlling premotor neurons in the rostral ventromedial medulla, including the raphe pallidus, that descend to provide the excitation of spinal circuits necessary to drive thermogenic thermal effectors. A distinct population of warm-sensitive preoptic neurons controls heat loss through an inhibitory input to raphe pallidus sympathetic premotor neurons controlling cutaneous vasoconstriction. The model proposed for central thermoregulatory control provides a useful platform for further understanding of the functional organization of central thermoregulation and elucidating the hypothalamic circuitry and neurotransmitters involved in body temperature regulation.

Mulder, N., Nembaware, V., Adekile, A., Anie, K. A., Inusa, B., Brown, B., et al. (2016). Proceedings of

a sickle cell disease ontology workshop - towards the first comprehensive ontology for sickle cell disease. *Applied and Translational Genomics,*

Sickle cell disease (SCD) is a debilitating single gene disorder caused by a single point mutation that results in physical deformation (i.e. sickling) of erythrocytes at reduced oxygen tensions. Up to 75% of SCD in newborns world-wide occurs in sub-Saharan Africa, where neonatal and

childhood mortality from sickle cell related complications is high. While SCD research across the globe is tackling the disease on multiple fronts, advances have yet to significantly impact on the health and quality of life of SCD patients, due to lack of coordination of these disparate efforts. Ensuring data across studies is directly comparable through standardization is a necessary step towards realizing this goal. Such a standardization requires the development and implementation of a disease-specific ontology for SCD that is applicable globally. Ontology development is best achieved by bringing together experts in the domain to contribute their knowledge. The SCD community and H3ABioNet members joined forces at a recent SCD Ontology workshop to develop an ontology covering aspects of SCD under the classes: phenotype, diagnostics, therapeutics, quality of life, disease modifiers and disease stage. The aim of the workshop was for participants to contribute their expertise to development of the structure and contents of the SCD ontology. Here we describe the proceedings of the Sickle Cell Disease Ontology Workshop held in Cape Town South Africa in February 2016 and its outcomes. The objective of the workshop was to bring together experts in SCD from around the world to contribute their expertise to the development of various aspects of the SCD ontology. © 2015 The Authors.

Muralimanoharan, S., Maloyan, A., & Myatt, L. (2016). Mitochondrial function and glucose metabolism in the placenta with 2 gestational diabetes mellitus: Role of MIR-143. *Clinical Science (London, England : 1979)*,

A predisposing factor for development of the hyperglycemic state of gestational diabetes mellitus (GDM) is obesity. We previously showed that increasing maternal obesity is associated with significant reductions in placental mitochondrial respiration. MicroRNA (miR)-143 has been previously shown to regulate the metabolic switch from oxidative phosphorylation to aerobic glycolysis in cancer tissues. We hypothesized that mitochondrial respiration is reduced and aerobic glycolysis is upregulated via changes in miR-143 expression in the placenta of women with GDM. Placental tissue was collected at term from women with A1GDM (controlled by diet), A2GDM (controlled by medication), and BMI-matched controls (CTRL). miR-143 expression was measured by RT-PCR. Expression of mitochondrial complexes, transcription factors PGC1alpha and PPARgamma, components of mTOR signaling, glucose transporter Glut1 and glycolytic enzymes (HK-2, PFK, and LDH) were measured by Western Blot. Trophoblast respiration was

measured by XF24 Analyzer. Expression of miR-143, mitochondrial complexes, and PPARgamma and PGC1alpha, which act downstream of miR-143, were significantly decreased in A2GDM placentae vs. A1GDM and CTRL ($p < 0.01$). Placental hPL levels, expression of glycolytic enzymes, Glut1 and mTOR signaling were also significantly increased by more than 2 fold in A2GDM vs A1GDM and CTRL ($p < 0.05$). There was a 50% reduction in mitochondrial respiration in trophoblast cells isolated from A2GDM placentae. Overexpression of miR-143 was able to increase mitochondrial respiration, increase protein expression of mitochondrial complexes, and decrease expression of glycolytic enzymes by 40% compared to A2GDM. Downregulation of miR-143 mediates the metabolic switch from oxidative phosphorylation to aerobic glycolysis in placenta of women with A2GDM.

Nabavizadeh, N., Elliott, D. A., Chen, Y., Kusano, A. S., Mitin, T., Thomas, C. R., J., et al. (2016).

Image guided radiation therapy (IGRT) practice patterns and IGRT's impact on workflow and treatment planning: Results from a national survey of american society for radiation oncology members. *International Journal of Radiation Oncology Biology Physics*, 94(4), 850-857.

Purpose To survey image guided radiation therapy (IGRT) practice patterns, as well as IGRT's impact on clinical workflow and planning treatment volumes (PTVs). Methods and Materials A sample of 5979 treatment site-specific surveys was e-mailed to the membership of the American Society for Radiation Oncology (ASTRO), with questions pertaining to IGRT modality/frequency, PTV expansions, method of image verification, and perceived utility/value of IGRT. On-line image verification was defined as images obtained and reviewed by the physician before treatment. Off-line image verification was defined as images obtained before treatment and then reviewed by the physician before the next treatment. Results Of 601 evaluable responses, 95% reported IGRT capabilities other than portal imaging. The majority (92%) used volumetric imaging (cone-beam CT [CBCT] or megavoltage CT), with volumetric imaging being the most commonly used modality for all sites except breast. The majority of respondents obtained daily CBCTs for head and neck intensity modulated radiation therapy (IMRT), lung 3-dimensional conformal radiation therapy or IMRT, anus or pelvis IMRT, prostate IMRT, and prostatic fossa IMRT. For all sites, on-line image verification was most frequently performed during the first few fractions only. No association was seen between IGRT frequency or CBCT utilization and clinical treatment volume to PTV

expansions. Of the 208 academic radiation oncologists who reported working with residents, only 41% reported trainee involvement in IGRT verification processes. Conclusion Consensus guidelines, further evidence-based approaches for PTV margin selection, and greater resident involvement are needed for standardized use of IGRT practices. © 2016 Elsevier Inc. All rights reserved.

Najjar, R. H., Docherty, A., & Miehl, N. (2016). Psychometric properties of an objective structured clinical assessment tool. *Clinical Simulation in Nursing, 12*(3), 88-95.

Background: Inconsistencies in approaches to clinical teaching and evaluation can lead to significant challenges in the absence of reliable, standardized assessment measures. The purpose of our research was to examine the psychometric properties of a rubric to evaluate students in a simulation testing environment. Method: Two raters used an evaluation rubric to score the performance of 33 students taking part in an objective structured clinical assessment (OSCA). Content validity and inter-rater reliability statistics were calculated. Results: The OSCA as a whole demonstrated excellent content validity and acceptable inter-reliability was obtained on the evaluation rubric. Conclusions: Given the right process, structure, and support, our results indicate that the OSCA is a robust and reliable approach to evaluate student clinical performance. © 2016 International Nursing Association for Clinical Simulation and Learning.

Nelson, H. D., Fu, R., Cantor, A., Pappas, M., Daeges, M., & Humphrey, L. (2016). Effectiveness of breast cancer screening: Systematic review and meta-analysis to update the 2009 U.S. preventive services task force recommendation. *Annals of Internal Medicine, 164*(4), 244-255.

Background: In 2009, the U.S. Preventive Services Task Force recommended biennial mammography screening for women aged 50 to 74 years and selective screening for those aged 40 to 49 years. Purpose: To review studies of the effectiveness of breast cancer screening in average-risk women. Data Sources: MEDLINE and Cochrane databases to 4 June 2015. Study Selection: English-language randomized, controlled trials and observational studies of screening with mammography, magnetic resonance imaging, and ultrasonography that reported breast cancer mortality, all-cause mortality, or advanced breast cancer outcomes. Data Extraction: Investigators extracted and confirmed data and dual rated study quality; discrepancies were

resolved through consensus. Data Synthesis: Fair-quality evidence from a meta-analysis of mammography trials indicated relative risks (RRs) for breast cancer mortality of 0.92 for women aged 39 to 49 years (95% CI, 0.75 to 1.02) (9 trials; 3 deaths prevented per 10 000 women over 10 years); 0.86 for those aged 50 to 59 years (CI, 0.68 to 0.97) (7 trials; 8 deaths prevented per 10 000 women over 10 years); 0.67 for those aged 60 to 69 years (CI, 0.54 to 0.83) (5 trials; 21 deaths prevented per 10 000 women over 10 years); and 0.80 for those aged 70 to 74 years (CI, 0.51 to 1.28) (3 trials; 13 deaths prevented per 10 000 women over 10 years). Risk reduction was 25% to 31% for women aged 50 to 69 years in observational studies of mammography screening. All-cause mortality was not reduced with screening. Advanced breast cancer was reduced for women aged 50 years or older (RR, 0.62 [CI, 0.46 to 0.83]) (3 trials) but not those aged 39 to 49 years (RR, 0.98 [CI, 0.74 to 1.37]) (4 trials); less evidence supported this outcome. Limitations: Most trials used imaging technologies and treatments that are now outdated, and definitions of advanced breast cancer were heterogeneous. Studies of effectiveness based on risk factors, intervals, or other modalities were unavailable or methodologically limited. Conclusion: Breast cancer mortality is generally reduced with mammography screening, although estimates are not statistically significant at all ages and the magnitudes of effect are small. Advanced cancer is reduced with screening for women aged 50 years or older. Primary Funding Source: Agency for Healthcare Research and Quality.

Nelson, H. D., O'Meara, E. S., Kerlikowske, K., Balch, S., & Miglioretti, D. (2016). Factors associated with rates of false-positive and false-negative results from digital mammography screening: An analysis of registry data. *Annals of Internal Medicine*, 164(4), 226-235.

Background: Women screened with digital mammography may receive false-positive and false-negative results and subsequent imaging and biopsies. How these outcomes vary by age, time since the last screening, and individual risk factors is unclear. Objective: To determine factors associated with false-positive and false-negative digital mammography results, additional imaging, and biopsies among a general population of women screened for breast cancer. Design: Analysis of registry data. Setting: Participating facilities at 5 U.S. Breast Cancer Surveillance Consortium breast imaging registries with linkages to pathology databases and tumor registries. Patients: 405 191 women aged 40 to 89 years screened with digital mammography between

2003 and 2011. A total of 2963 were diagnosed with invasive cancer or ductal carcinoma in situ within 12 months of screening. Measurements: Rates of false-positive and false-negative results and recommendations for additional imaging and biopsies from a single screening round; comparisons by age, time since the last screening, and risk factors. Results: Rates of false-positive results (121.2 per 1000 women [95% CI, 105.6 to 138.7]) and recommendations for additional imaging (124.9 per 1000 women [CI, 109.3 to 142.3]) were highest among women aged 40 to 49 years and decreased with increasing age. Rates of false-negative results (1.0 to 1.5 per 1000 women) and recommendations for biopsy (15.6 to 17.5 per 1000 women) did not differ greatly by age. Results did not differ by time since the last screening. False-positive rates were higher for women with risk factors, particularly family history of breast cancer; previous benign breast biopsy result; high breast density; and, for younger women, low body mass index. Limitations: Confounding by variation in patient-level characteristics and outcomes across registries and regions may have been present. Some factors, such as numbers of first- and second-degree relatives with breast cancer and diagnoses associated with previous benign biopsy results, were not examined. Conclusion: False-positive mammography results and additional imaging are common, particularly for younger women and those with risk factors, whereas biopsies occur less often. Rates of false-negative results are low. Primary Funding Source: Agency for Healthcare Research and Quality and National Cancer Institute.

Nelson, H. D., Pappas, M., Cantor, A., Griffin, J., Daeges, M., & Humphrey, L. (2016). Harms of breast cancer screening: Systematic review to update the 2009 U.S. preventive services task force recommendation. *Annals of Internal Medicine*, 164(4), 256-267.

Background: In 2009, the U.S. Preventive Services Task Force recommended biennial mammography screening for women aged 50 to 74 years and selective screening for those aged 40 to 49 years. Purpose: To review studies of screening in average-risk women with mammography, magnetic resonance imaging, or ultrasonography that reported on false-positive results, overdiagnosis, anxiety, pain, and radiation exposure. Data Sources: MEDLINE and Cochrane databases through December 2014. Study Selection: English-language systematic reviews, randomized trials, and observational studies of screening. Data Extraction: Investigators extracted and confirmed data from studies and dual-rated study quality. Discrepancies were

resolved through consensus. Data Synthesis: Based on 2 studies of U.S. data, 10-year cumulative rates of false-positive mammography results and biopsies were higher with annual than biennial screening (61% vs. 42% and 7% vs. 5%, respectively) and for women aged 40 to 49 years, those with dense breasts, and those using combination hormone therapy. Twenty-nine studies using different methods reported overdiagnosis rates of 0% to 54%; rates from randomized trials were 11% to 22%. Women with false-positive results reported more anxiety, distress, and breast cancer-specific worry, although results varied across 80 observational studies. Thirty-nine observational studies indicated that some women reported pain during mammography (1% to 77%); of these, 11% to 46% declined future screening. Models estimated 2 to 11 screening-related deaths from radiation-induced cancer per 100 000 women using digital mammography, depending on age and screening interval. Five observational studies of tomosynthesis and mammography indicated increased biopsies but reduced recalls compared with mammography alone. Limitations: Studies of overdiagnosis were highly heterogeneous, and estimates varied depending on the analytic approach. Studies of anxiety and pain used different outcome measures. Radiation exposure was based on models. Conclusion: False-positive results are common and are higher for annual screening, younger women, and women with dense breasts. Although overdiagnosis, anxiety, pain, and radiation exposure may cause harm, their effects on individual women are difficult to estimate and vary widely. Primary Funding Source: Agency for Healthcare Research and Quality.

Newgard, C. D., Fu, R., Zive, D., Rea, T., Malveau, S., Daya, M., et al. (2016). Prospective validation of the national field triage guidelines for identifying seriously injured persons. *Journal of the American College of Surgeons*, 222(2), 146-158e2.

Background The national field trauma triage guidelines have been widely implemented in US trauma systems, but never prospectively validated. We sought to prospectively validate the guidelines, as applied by out-of-hospital providers, for identifying high-risk trauma patients.

Study Design This was an out-of-hospital prospective cohort study from January 1, 2011 through December 31, 2011 with 44 Emergency Medical Services agencies in 7 counties in 2 states. We enrolled injured patients transported to 28 acute care hospitals, including 7 major trauma centers (Level I and II trauma hospitals) and 21 nontrauma hospitals. The primary exposure term was

Emergency Medical Services' use of one or more field triage criteria in the national field triage guidelines. Outcomes included Injured Severity Score ≥ 16 (primary) and critical resource use within 24 hours of emergency department arrival (secondary). Results We enrolled 53,487 injured children and adults transported by Emergency Medical Services to an acute care hospital, 17,633 of which were sampled for the primary analysis; 13.9% met field triage guidelines, 3.1% had Injury Severity Score ≥ 16 , and 1.7% required early critical resources. The sensitivity and specificity of the field triage guidelines were 66.2% (95% CI, 60.2-71.7%) and 87.8% (95% CI, 87.7-88.0%) for Injury Severity Score ≥ 16 and 80.1% (95% CI, 65.8-89.4%) and 87.3% (95% CI 87.1-87.4%) for early critical resource use. Triage guideline sensitivity decreased with age, from 87.4% in children to 51.8% in older adults. Conclusions The national field triage guidelines are relatively insensitive for identifying seriously injured patients and patients requiring early critical interventions, particularly among older adults. © 2016 American College of Surgeons.

Newgard, C. D., & Lowe, R. A. (2016). Cost savings in trauma systems: The devil's in the details. *Annals of Emergency Medicine, 67*(1), 68-70.

Ng, J. K., Stout, A. U., Aaby, A. A., & Ng, J. D. (2015). Blepharophimosis syndrome with absent tear production. *Ophthalmic Plastic and Reconstructive Surgery, 31*(3), e62.

The purpose of this report was to present a case of congenital alacrima in a patient with blepharophimosis-ptosis-epicanthus inversus syndrome (BPES). A 9-month-old boy presented with characteristic clinical findings of BPES confirmed by genetic testing. On further history taking and evaluation, the patient was noted to have no tear production, despite clinically present palpebral lobes of the lacrimal glands. BPES is an autosomal dominant condition characterized by narrowed horizontal palpebral fissures, severe bilateral symmetric ptosis, epicanthus inversus, and telecanthus. To the authors' knowledge, this represents the second reported case of congenital alacrima in this syndrome. The first case described in the literature was in a 9-month-old girl who had congenital absence of the lacrimal glands. BPES may present with alacrima requiring vigilant lifelong lubrication and careful consideration in decisions for eyelid surgery including ptosis repair.

Ngamcherdtrakul, W., Castro, D. J., Gu, S., Morry, J., Reda, M., Gray, J. W., et al. (2016). Current development of targeted oligonucleotide-based cancer therapies: Perspective on HER2-positive breast cancer treatment. *Cancer Treatment Reviews, 45*, 19-29.

This Review discusses the various types of non-coding oligonucleotides, which have garnered extensive interest as new alternatives for targeted cancer therapies over small molecule inhibitors and monoclonal antibodies. These oligonucleotides can target any hallmark of cancer, no longer limited to so-called "druggable" targets. Thus, any identified gene that plays a key role in cancer progression or drug resistance can be exploited with oligonucleotides. Among them, small-interfering RNAs (siRNAs) are frequently utilized for gene silencing due to the robust and well established mechanism of RNA interference. Despite promising advantages, clinical translation of siRNAs is hindered by the lack of effective delivery platforms. This Review provides general criteria and consideration of nanoparticle development for systemic siRNA delivery. Different classes of nanoparticle candidates for siRNA delivery are discussed, and the progress in clinical trials for systemic cancer treatment is reviewed. Lastly, this Review presents HER2 (human epidermal growth factor receptor type 2)-positive breast cancer as one example that could benefit significantly from siRNA technology. How siRNA-based therapeutics can overcome cancer resistance to such therapies is discussed.

Nichol, J. R., Fu, R., French, K., Momberger, J., & Handel, D. A. (2016). Association between patient and emergency department operational characteristics and patient satisfaction scores in a pediatric population. *Pediatric Emergency Care, 32*(3), 139-141.

BACKGROUND: Emergency departments (EDs) are seeing an increase in the importance of patient satisfaction scores, yet little is known about their association with patient and operational characteristics. **OBJECTIVES:** This study aimed to identify patient and operational characteristics associated with patient satisfaction scores. **METHODS:** This was a retrospective analysis of data from Press Ganey patient satisfaction surveys of pediatric patients (2 hours) was significantly associated with lower scores in overall experience and likelihood to recommend, whereas surveys completed online had higher scores for waiting time to see a provider compared with mailed. **CONCLUSIONS:** Emergency departments looking to increase satisfaction scores should focus efforts on decreasing door-to-room times.

Nielson, C. M., Jones, K. S., Chun, R. F., Jacobs, J., Wang, Y., Hewison, M., et al. (2016). Role of assay type in determining free 25-hydroxyvitamin D levels in diverse populations. *The New England Journal of Medicine*,

To the Editor: It is unclear whether circulating free or bioavailable 25-hydroxyvitamin D is a better marker of vitamin D status than is total 25-hydroxyvitamin D, especially in racially diverse populations. Until recently, the only method to compare the levels was to estimate the level of free or bioavailable 25-hydroxyvitamin D from total 25-hydroxyvitamin D, vitamin D-binding protein (also known as gc-globulin, encoded by the GC gene), and albumin, with or without the GC genotype. Powe et al. reported that levels of vitamin D-binding protein, as measured on a monoclonal enzyme-linked immunosorbent assay (ELISA, R&D Systems), were lower in black . . .

Noguchi, K. K., Johnson, S. A., Kristich, L. E., Martin, L. D., Dissen, G. A., Olsen, E. A., et al. (2016). Lithium protects against anaesthesia neurotoxicity in the infant primate brain. *Scientific Reports*, 6, 22427.

Exposure of infant animals, including non-human primates (NHPs), to anaesthetic drugs causes apoptotic death of neurons and oligodendrocytes (oligos) and results in long-term neurodevelopmental impairment (NDI). Moreover, retrospective clinical studies document an association between anaesthesia exposure of human infants and significant increase in NDI. These findings pose a potentially serious dilemma because millions of human infants are exposed to anaesthetic drugs every year as part of routine medical care. Lithium (Li) at clinically established doses is neuroprotective in various cerebral injury models. We therefore investigated whether Li also protects against anaesthesia neurotoxicity in infant NHPs. On postnatal day 6 NHPs were anaesthetized with the widely used anaesthetic isoflurane (ISO) for 5 h employing the same standards as in a human pediatric surgery setting. Co-administration of Li completely prevented the acute ISO-induced neuroapoptosis and significantly reduced ISO-induced apoptosis of oligodendroglia. Our findings are highly encouraging as they suggest that a relatively simple pharmacological manipulation might protect the developing primate brain against the neurotoxic action of anaesthetic drugs while not interfering with the beneficial actions of these drugs. Further research is needed to determine Li's potential to prevent long-term NDI resulting from ISO anaesthesia, and to establish its safety in human infants.

Nolz, J. C., & Hill, A. B. (2016). Strength in numbers: Visualizing CTL-mediated killing in vivo.

Immunity, 44(2), 207-208.

Cytotoxic CD8+ T lymphocytes (CTLs) have long been believed to be extremely efficient killers. Forster and colleagues (Halle et al., 2016) used in vivo imaging to tell a different story, in which each CTL killed only 2-16 targets a day, and several CTLs per target were needed to get the job done. © 2016 Elsevier Inc.

Noone, J., Sullivan, M., McKinnis, N. C., Allen, T. L., Regalado, C., & Esqueda, T. (2016). Latino youth participation in community-based participatory research to reduce teen pregnancy disparities.

Children and Youth Services Review, 63, 36-39.

Background: Community-based participatory research can provide a framework to build community capacity to do health equity research, particularly from community members who may not typically participate in research design and intervention. Purpose: The purpose of this paper is to describe a community-based coalition's partnership and engagement with Latino youth throughout the research process addressing health disparities in unintended teen pregnancy rates in a local community. Israel and colleagues' components of CBPR provide a framework to develop youth participation throughout the research process. Method: High school and college Latino youth participated in health equity research from community assessments to design an intervention and dissemination of results. Results: Working with youth can improve the integrity and validity of the research process and can also provide benefits to the community and individual youth members, resulting in increased community capacity for health equity research. Discussion: Lessons learned about the direct and indirect benefits and challenges are presented. Community-based partnerships working with youth should consider documenting the individual and collective impact of community engagement on the youth from the onset of participation. © 2016 Elsevier Ltd.

Norbury, J. W., Schimmerling, W., Slaba, T. C., Azzam, E. I., Badavi, F. F., Baiocco, G., et al. (2016).

Galactic cosmic ray simulation at the NASA space radiation laboratory. *Life Sciences in Space Research*, 8, 38-51.

Most accelerator-based space radiation experiments have been performed with single ion beams

at fixed energies. However, the space radiation environment consists of a wide variety of ion species with a continuous range of energies. Due to recent developments in beam switching technology implemented at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), it is now possible to rapidly switch ion species and energies, allowing for the possibility to more realistically simulate the actual radiation environment found in space. The present paper discusses a variety of issues related to implementation of galactic cosmic ray (GCR) simulation at NSRL, especially for experiments in radiobiology. Advantages and disadvantages of different approaches to developing a GCR simulator are presented. In addition, issues common to both GCR simulation and single beam experiments are compared to issues unique to GCR simulation studies. A set of conclusions is presented as well as a discussion of the technical implementation of GCR simulation.

Novak, M. A., Menard, M. T., El-Mallah, S. N., Rosenberg, K., Lutz, C. K., Worlein, J., et al. (2016).

Assessing significant (>30%) alopecia as a possible biomarker for stress in captive rhesus monkeys (*macaca mulatta*). *American Journal of Primatology*,

Hair loss is common in macaque colonies. Very little is known about the relationship between psychological stress and hair loss. We initially examined alopecia and hair cortisol concentrations in 198 (89 male) rhesus macaques from three primate centers and demonstrated replicability of our previous finding that extensive alopecia (>30% hair loss) is associated with increased chronic cortisol concentrations and significantly affected by facility. A subset of these monkeys (142 of which 67 were males) were sampled twice approximately 8 months apart allowing us to examine the hypotheses that gaining hair should be associated with decreases in cortisol concentrations and vice versa. Hair loss was digitally scored using ImageJ software for the first sample. Then visual assessment was used to examine the second sample, resulting in three categories of coat condition: (i) monkeys that remained fully haired; (ii) monkeys that remained alopecic (with more than 30% hair loss); or (iii) monkeys that showed more than a 15% increase in hair. The sample size for the group that lost hair was too small to be analyzed. Consistent with our hypothesis, monkeys that gained hair showed a significant reduction in hair cortisol concentrations but this effect only held for females. Coat condition changed little across sampling periods with only 25 (11 male) monkeys showing a greater than 15% gain of hair. Twenty (7

male) monkeys remained alopecic, whereas 97 (49 males) remained fully haired. Hair cortisol was highly correlated across samples for the monkeys that retained their status (remained alopecic or retained their hair). *Am. J. Primatol.* (c) 2016 Wiley Periodicals, Inc.

Novosad, D., Banfe, S., Britton, J., & Bloom, J. D. (2016). Conditional release placements of insanity acquittees in oregon: 2012-2014. *Behavioral Sciences and the Law*,
Between January 1, 2012 and December 31, 2014, there was a large population (N=200) of insanity acquittees placed on conditional release (CR) in the state of Oregon. This article looks at the demographic and system characteristics of this large group of individuals. The authors then focus on the initial housing placement and what happens to individuals after their release in relation to their housing placement. In Oregon, insanity acquittees are either conditionally released directly by the court or placed in the hospital prior to potential CR by a supervising board. In general, once CR occurs, individuals tend to stay in their initial placement without moving to less structured levels of care, raising concerns about transinstitutionalization. This is especially true for individuals released to the most structured living arrangement (secure residential treatment facility). Those individuals who are conditionally released to less structured settings have a higher rate of revocation back to the hospital. Those individuals who do move to less structured levels of care usually have longer hospital stays and start off in more structured levels of care to start their CR. © 2016 John Wiley & Sons, Ltd.

Novosad, S. A., Beekmann, S. E., Polgreen, P. M., Mackey, K., & Winthrop, K. L. (2016). Treatment of mycobacterium abscessus infection. *Emerging Infectious Diseases*, 22(3), 511-514.
Mycobacterium abscessus is often resistant to multiple antimicrobial drugs, and data supporting effective drugs or dosing regimens are limited. To better identify treatment approaches and associated toxicities, we collected a series of case reports from the Emerging Infections Network. Side effects were common and often led to changing or discontinuing therapy. © 2016, Centers for Disease Control and Prevention (CDC). All rights reserved.

Obrebsky, W., Agel, J., Archer, K., To, P., Tornetta, P., III, Bhandari, M., et al. (2016). Character, incidence, and predictors of knee pain and activity after infrapatellar intramedullary nailing of an isolated tibia fracture. *Journal of Orthopaedic Trauma*, 30(3), 135-141.

Objective: To study the activity and incidence of knee pain after sustaining an isolated tibia fracture treated with an infrapatellar intramedullary nail at 1 year. Design: Retrospective review of prospective cohort. Setting: Multicenter Academic and Community hospitals. Patients: Four hundred thirty-seven patients with an isolated tibia fracture completed a 12-month assessment on pain and self-reported activity. Intervention: Infrapatellar intramedullary nail. Outcomes: Demographic information, comorbid conditions, injury characteristics, and surgical technique were recorded. Knee pain was defined on a 1-7 scale with 1 being "no pain" and 7 being a "very great deal of pain." Knee pain >4 was considered clinically significant. Patients reported if they were "able," "able with difficulty," or "unable" to perform the following activities: kneel, run, climb stairs, and walk prolonged. Variables were tested in multilevel multivariable regression analyses. Results: In knee pain, 11% of patients reported a "good deal" to a "very great deal" of pain (>4), and 52% of patients reported "no" or "very little" pain at 12 months. In activity at 12 months, 26% and 29% of patients were unable to kneel or run, respectively, and 31% and 35% of patients, respectively, stated they were able with difficulty or unable to use stairs or walk. Conclusions: Clinically significant knee pain (>4/7) was present in 11% of patients 1 year after a tibia fracture. Of note, 31%-71% of patients had difficulty performing or were unable to perform routine daily activities of kneeling, running, and stair climbing, or walking prolonged distances. © Copyright 2015 Wolters Kluwer Health, Inc. All rights reserved.

Olson, R., Thompson, S. V., Wipfli, B., Hanson, G., Elliot, D. L., Anger, W. K., et al. (2016). Sleep, dietary, and exercise behavioral clusters among truck drivers with obesity: Implications for interventions. *Journal of Occupational and Environmental Medicine / American College of Occupational and Environmental Medicine*, 58(3), 314-321.

OBJECTIVE: The objectives of the study were to describe a sample of truck drivers, identify clusters of drivers with similar patterns in behaviors affecting energy balance (sleep, diet, and exercise), and test for cluster differences in health safety, and psychosocial factors. METHODS: Participants' (n = 452, body mass index M = 37.2, 86.4% male) self-reported behaviors were dichotomized prior to hierarchical cluster analysis, which identified groups with similar behavior covariation. Cluster differences were tested with generalized estimating equations. RESULTS: Five behavioral clusters were identified that differed significantly in age, smoking status, diabetes

prevalence, lost work days, stress, and social support, but not in body mass index. Cluster 2, characterized by the best sleep quality, had significantly lower lost workdays and stress than other clusters. CONCLUSIONS: Weight management interventions for drivers should explicitly address sleep, and may be maximally effective after establishing socially supportive work environments that reduce stress exposures.

Olson, R., Varga, A., Cannon, A., Jones, J., Gilbert-Jones, I., & Zoller, E. (2016). Toolbox talks to prevent construction fatalities: Empirical development and evaluation. *Safety Science*, 86, 122-131.

Three studies were conducted to develop and evaluate safety toolbox talks about fatal construction incidents. Study 1 surveyed workers (n = 28) about existing pre-shift meetings. An evidence-based structure for toolbox talks was developed, and study 2 evaluated our selected line drawing illustration format with workers (n = 30). Study 3 evaluated supervisors' talks using: (1) new toolbox guides and (2) long-form investigation reports with workers from eight construction crews. In study 1, 25% of the sample reported never conducted safety meetings. In study 2, compared to photos, line drawings increased the distance workers' could correctly identify hazards by over 1.5 m. In study 3, the new format was preferred by 82% of supervisors, saved them 15 min preparation/presentation time, and produced favorable impacts with workers. Brief scripted toolbox talks made it easier for supervisors to share fatal stories and prevention recommendations with their crews. When the format includes scripted text for the supervisors, prompts for discussion and action items, and line drawings worker understanding can be enhanced. © 2016 Elsevier Ltd.

Onega, T., Reisch, L. M., Frederick, P. D., Geller, B. M., Nelson, H. D., Lott, J. P., et al. (2016). Use of digital whole slide imaging in dermatopathology. *Journal of Digital Imaging*, 29(2), 243-253. Digital whole slide imaging (WSI) is an emerging technology for pathology interpretation, with specific challenges for dermatopathology, yet little is known about pathologists'™ practice patterns or perceptions regarding WSI for interpretation of melanocytic lesions. A national sample of pathologists (N = 207) was recruited from 864 invited pathologists from ten US states (CA, CT, HI, IA, KY, LA, NJ, NM, UT, and WA). Pathologists who had interpreted melanocytic lesions in the

past year were surveyed in this cross-sectional study. The survey included questions on pathologists'™ experience, WSI practice patterns and perceptions using a 6-point Likert scale. Agreement was summarized with descriptive statistics to characterize pathologists'™ use and perceptions of WSI. The majority of participating pathologists were between 40 and 59 years of age (62%) and not affiliated with an academic medical center (71%). Use of WSI was seen more often among dermatopathologists and participants affiliated with an academic medical center. Experience with WSI was reported by 41% , with the most common type of use being for education and testing (CME, board exams, and teaching in general, 71%), and clinical use at tumor boards and conferences (44%). Most respondents (77%) agreed that accurate diagnoses can be made with this technology, and 59% agreed that benefits of WSI outweigh concerns. However, 78% of pathologists reported that digital slides are too slow for routine clinical interpretation. The respondents were equally split as to whether they would like to adopt WSI (49%) or not (51%). The majority of pathologists who interpret melanocytic lesions do not use WSI, but among pathologists who do, use is largely for CME, licensure/board exams, and teaching. Positive perceptions regarding WSI slightly outweigh negative perceptions. Understanding practice patterns with WSI as dissemination advances may facilitate concordance of perceptions with adoption of the technology. © 2015, Society for Imaging Informatics in Medicine.

Orb, Q., Mace, J. C., Deconde, A. S., Steele, T. O., Cox, S. T., Smith, T. L., et al. (2016). Patients electing medical vs surgical treatment: Emotional domain of the rhinosinusitis disability index associates with treatment selection. *International Forum of Allergy and Rhinology*, 6(3), 315-321. Background: The Rhinosinusitis Disability Index (RSDI) consists of multiple subdomains shown to be useful in studying chronic rhinosinusitis (CRS). The objective of this study was to determine if RSDI subdomain scores are associated with selection of treatment modality (endoscopic sinus surgery ESS] or continued medical management CMM]) in subjects with CRS. Methods: Patients with CRS were prospectively enrolled into a multi-institutional cohort study. Following an initial period of medical management, patients elected to undergo treatment with either ESS or CMM. Baseline RSDI total and subdomain scores were compared between patients electing different treatment modalities. Results: A total of 684 subjects were enrolled with 122 (17.8%) electing

CMM and 562 (82.2%) electing ESS. When compared to patients undergoing CMM, patients electing ESS exhibited significantly higher mean baseline RSDI total scores (mean $\hat{\pm}$ standard deviation SD]: 48.1 $\hat{\pm}$ 24.9 vs 40.1 $\hat{\pm}$ 24.1; $p = 0.001$) and subdomain scores (emotional: 13.2 $\hat{\pm}$ 9.1 vs 10.4 $\hat{\pm}$ 8.3; $p = 0.001$; functional: 15.3 $\hat{\pm}$ 8.9 vs 12.6 $\hat{\pm}$ 8.4; $p = 0.002$; and physical: 19.6 $\hat{\pm}$ 9.3 vs 17.1 $\hat{\pm}$ 9.6; $p = 0.007$). Emotional subdomain scores were found to be the most associated with choice of treatment modality. Conclusion: Patients with CRS electing ESS had worse baseline RSDI total and subdomain scores compared to those electing CMM. Although both rhinologic and nonrhinologic symptoms contributed to the selection of treatment modality, emotional symptoms appeared to exhibit the greatest influence on patient-centered treatment decisions. © 2016 ARS-AAOA, LLC.

Ormseth, M. J., Yancey, P. G., Solus, J. F., Bridges, S. L., Jr, Curtis, J. R., Linton, M. F., et al. (2016).

Effect of drug therapy on net cholesterol efflux capacity of HDL-enriched serum in rheumatoid arthritis. *Arthritis & Rheumatology (Hoboken, N.J.)*,

BACKGROUND: Patients with rheumatoid arthritis (RA) have increased coronary heart disease (CHD) risk. Some RA therapies may modify this risk, but underlying mechanisms are unclear.

HDL's cholesterol efflux capacity is associated with reduced CHD risk in non-RA populations; however, inflammation may impair HDL's function. We hypothesized that reduced inflammation

from treatment with methotrexate (MTX), adalimumab (ADA) and tocilizumab (TOC) would increase net cholesterol efflux capacity (CEC) of HDL in patients with RA. METHODS: A

longitudinal multi-center study (Treatment Efficacy and Toxicity in Rheumatoid Arthritis Database and Repository) provided clinical information and serum samples from 70 patients with RA before

and 6 months after starting a new drug (MTX (n=23), ADA (n=22), and TOC (n=25)). Disease

activity was measured by DAS28-ESR. Net CEC was measured in paired serum samples using

THP-1 macrophages with fluorometric assay for cholesterol measurement. RESULTS: DAS28-ESR

decreased with all treatments ($P < 0.05$). CONCLUSION: HDL's net CEC did not change significantly

after 6 months of new RA therapy, except in those with impaired baseline CEC receiving TOC.

Change in disease activity was associated with change in net CEC. This article is protected by

copyright. All rights reserved.

Orwoll, E. S. (2016). Establishing a framework--does testosterone supplementation help older men? *The New England Journal of Medicine*, 374(7), 682-683.

Overton, J. A., Dietze, H., Essaid, S., Osumi-Sutherland, D., & Mungall, C. J. (2015). ROBOT: A command-line tool for ontology development. , 1515.

ROBOT is a command-line tool for working with ontologies, especially Open Biomedical Ontologies. It builds on OWLAPI and is designed to eventually replace Oort and many functions of OWLTools. Currently implemented commands include: reporting on differences between ontologies, merging ontologies, extracting ontology modules, filtering ObjectProperties, and reasoning. Commands can be chained together to form powerful, repeatable workflows. ROBOT is in early development but is available for use under an open source (BSD) license. Â© Copyright 2015 for this paper by its authors.

Palucka, A. K., & Coussens, L. M. (2016). The basis of oncoimmunology. *Cell*, 164(6), 1233-1247.

Cancer heterogeneity, a hallmark enabling clonal survival and therapy resistance, is shaped by active immune responses. Antigen-specific T cells can control cancer, as revealed clinically by immunotherapeutics such as adoptive T-cell transfer and checkpoint blockade. The host immune system is thus a powerful tool that, if better harnessed, could significantly enhance the efficacy of cytotoxic therapy and improve outcomes for cancer sufferers. To realize this vision, however, a number of research frontiers must be tackled. These include developing strategies for neutralizing tumor-promoting inflammation, broadening T-cell repertoires (via vaccination), and elucidating the mechanisms by which immune cells organize tumor microenvironments to regulate T-cell activity. Such efforts will pave the way for identifying new targets for combination therapies that overcome resistance to current treatments and promote long-term cancer control. Â© 2016 Elsevier Inc.

Pasadhika, S., & Rosenbaum, J. T. (2016). Crohn's disease and ulcerative colitis. (pp. 719-729) Springer Berlin Heidelberg.

Inflammatory bowel disease (IBD) comprises two major immune-mediated disorders: ulcerative colitis (UC) and Crohn's disease (CD). These disorders have distinct pathologic and clinical

characteristics. Extraintestinal manifestations including ocular involvement can be present in both diseases. © Springer-Verlag Berlin Heidelberg 2016.

Patel, A. K., Newcomb, C. W., Liesegang, T. L., Pujari, S. S., Suhler, E. B., Thorne, J. E., et al. (2016).

Risk of retinal neovascularization in cases of uveitis. *Ophthalmology*, 123(3), 646-654.

Purpose To evaluate the risk of and risk factors for retinal neovascularization (NV) in cases of uveitis. **Design** Retrospective cohort study. **Participants** Patients with uveitis at 4 US academic ocular inflammation subspecialty practices. **Methods** Data were ascertained by standardized chart review. Prevalence data analysis used logistic regression. Incidence data analysis used survival analysis with time-updated covariates where appropriate. **Main Outcome Measures** Prevalence and incidence of NV. **Results** Among uveitic eyes of 8931 patients presenting for initial evaluation, 106 of 13 810 eyes had NV (prevalence = 0.77%, 95% confidence interval [CI], 0.60-0.90). Eighty-eight more eyes developed NV over 26 465 eye-years (incidence, 0.33%/eye-year; 95% CI, 0.27-0.41). Factors associated with incident NV include age 35 years (adjusted hazard ratio [aHR], 2.4; 95% CI, 1.5-3.9), current cigarette smoking (aHR, 1.9; 95% CI, 1.1-3.4), and systemic lupus erythematosus (aHR, 3.5, 95% CI, 1.1-11). Recent diagnosis of uveitis was associated with an increased incidence of NV (compared with patients diagnosed >5 years ago, aHR, 2.4 95% CI, 1.1-5.0] and aHR, 2.6 95% CI, 1.2-6.0] for diagnosis within <1 year vs. 1-5 years, respectively). Compared with anterior uveitis, intermediate uveitis (aHR, 3.1; 95% CI, 1.5-6.6), posterior uveitis (aHR, 5.2; 95% CI, 2.5-11), and panuveitis (aHR, 4.3; 95% CI, 2.0-9.3) were associated with a similar degree of increased NV incidence. Active (aHR, 2.1, 95% CI, 1.2-3.7) and slightly active (aHR, 2.4, 95% CI, 1.3-4.4) inflammation were associated with an increased incidence of NV compared with inactive inflammation. Neovascularization incidence also was increased with retinal vascular occlusions (aHR, 10, 95% CI, 3.0-33), retinal vascular sheathing (aHR, 2.6, 95% CI, 1.4-4.9), and exudative retinal detachment (aHR, 4.1, 95% CI, 1.3-13). Diabetes mellitus was associated with a somewhat increased incidence of retinal NV (aHR, 2.3, 95% CI, 1.1-4.9), and systemic hypertension (aHR 1.5, 95% CI, 0.89-2.4) was associated with nonsignificantly increased NV incidence. Results were similar in sensitivity analyses excluding the small minority of patients with diabetes mellitus. **Conclusions** Retinal NV is a rare complication of uveitis, which occurs more frequently in younger patients, smokers, and

those with intermediate/posterior/panuveitis, systemic vasculopathy, retinal vascular disease, or active inflammation. Inflammation and retinal NV likely are linked; additional studies are needed to further elucidate this connection. © 2016 American Academy of Ophthalmology.

Patel, C., Omer, E., Diamond, S. J., & McClave, S. A. (2016). Can nutritional assessment tools predict response to nutritional therapy? *Current Gastroenterology Reports*, 18(4), 15-016-0488-y.

Traditional tools and scoring systems for nutritional assessment have focused solely on parameters of poor nutritional status in the past, in an effort to define the elusive concept of malnutrition. Such tools fail to account for the contribution of disease severity to overall nutritional risk. High nutritional risk, caused by either deterioration of nutritional status or greater disease severity (or a combination of both factors), puts the patient in a metabolic stress state characterized by adverse outcome and increased complications. Newer scoring systems for determining nutritional risk, such as the Nutric Score and the Nutritional Risk Score-2002 have created a paradigm shift connecting assessment and treatment with quality outcome measures of success. Clinicians now have the opportunity to identify high risk patients through their initial assessment, provide adequate or sufficient nutrition therapy, and expect improved patient outcomes as a result. These concepts are supported by observational and prospective interventional trials. Greater clinical experience and refinement in these scoring systems are needed in the future to optimize patient response to nutrition therapy.

Patel, M. S., Raza, S. S., Bhakta, A., Ewing, T., Bukur, M., Vagefi, P. A., et al. (2016). Patients on state organ donor registries receive similar levels of intensive care compared to those who are not: An opportunity to increase public intent to donate. *Clinical Transplantation*,

The intent to donate organs is affected by the public perception that patients on state registries receive less aggressive life-saving care in order to allow organ donation to proceed. However, the association between first person authorization to donate organs and the actual care received by eventual organ donors in hospitals is unknown. From August 2010 to April 2011, all eight OPOs in UNOS Region 5 prospectively recorded demographic data and organ utilization rates on all donors after neurologic determination of death (DNDDs). Critical care and physiologic parameters were also recorded at referral for imminent neurologic death and prior to authorization for donation to

reflect the aggressiveness of provided care. There were 586 DNDDs and 23% were on a state registry. Compared to non-registered DNDDs, those on state registries were older but were noted to have similar critical care parameters at both referral and authorization. Furthermore, there was no significant difference in organs procured per donor or organs transplanted per donor between registered and non-registered DNDDs. Thus, DNDDs who are on state donor registries receive similar levels of intensive care compared to non-registered donors. The association noted in this study, may therefore help to dispel a common misperception that decreases the intent to donate. This article is protected by copyright. All rights reserved.

Patil, E., Darney, B., Orme-Evans, K., Beckley, E. H., Bergander, L., Nichols, M., et al. (2016).

Aspiration abortion with immediate intrauterine device insertion: Comparing outcomes of advanced practice clinicians and physicians. *Journal of Midwifery and Women's Health*,
Introduction: Immediate postabortion intrauterine device (IUD) insertion is a safe, effective strategy to prevent subsequent unplanned pregnancy. Oregon is one of 5 US states where advanced practice clinicians perform aspiration abortions. This study compares outcomes of first-trimester aspiration abortion with immediate IUD insertion between advanced practice clinicians and physicians. Methods: We conducted a historical cohort study of first-trimester aspiration abortions with immediate IUD insertion performed at our center from 2009 to 2011. We extracted demographic and clinical data from patient charts. Immediate complications including excessive blood loss, perforation, and reaspirations were recorded at the time of procedure. We used descriptive statistics and multivariable logistic regression to test for differences in outcomes by clinician type. Results: Data were available on 669 of the 1134 combined procedures. Advanced practice clinicians performed 224 of these. There were no significant differences in immediate outcomes. The only immediate complications were reaspirations; 1.8% (4/224) in the advanced practice clinician group, and 2.0% (9/445) in the physician group ($P = .83$). Discussion: We found no differences in outcomes between provider type for immediate IUD insertion after first-trimester aspiration abortion. This study helps reinforce that advanced practice clinicians can provide immediate postaspiration abortion IUD insertions with similar outcomes to those of physicians. Many countries do not allow advanced practice clinicians to perform this service, but a

change in policy could help address family planning provider shortages. © 2016 by the American College of Nurse-Midwives.

Patil, E., & Jensen, J. T. (2016). Permanent contraception for women. *Seminars in Reproductive Medicine,*

Permanent contraception is a highly desired and commonly used contraceptive option for women around the world who desire never to become pregnant. Current methods of female permanent contraception require surgery. Postpartum tubal ligation and interval surgical tubal ligation are safe and effective, do not interfere with menstrual cycles, and require no ongoing cost or medical checkups. Hysteroscopic tubal occlusion offers a less invasive surgical approach, but requires an imaging study for verification of correct placement. However, not all women have access to a surgeon trained to provide permanent contraception, or they may face other prohibitive logistic or financial burdens. The development of novel permanent contraception methods that are immediately effective and/or nonsurgical could help improve access to and acceptability of permanent contraception. The expansion of permanent contraception options could help women achieve their family planning goals and reduce unintended pregnancies.

Phan, D., Narayanan, K., Uy-Evanado, A., Teodorescu, C., Reinier, K., Chugh, H., et al. (2016). T-wave reversal in the augmented unipolar right arm electrocardiographic lead is associated with increased risk of sudden death. *Journal of Interventional Cardiac Electrophysiology, 45(2), 141-147.*

Background: Repolarization abnormalities are associated with ventricular arrhythmias, and published studies report that a reversal of T wave polarity (positive or flat T wave) in lead aVR may be linked to increased cardiovascular mortality. We evaluated whether a positive or flat T wave in aVR is a risk marker for sudden cardiac death (SCD). Methods: SCD cases from the Oregon Sudden Unexpected Death Study (catchment population ~1 million) were compared to geographic controls with coronary artery disease and no history of SCD. Archived electrocardiograms performed prior and unrelated to the SCD event were evaluated. Results: SCD cases (n = 691, 67.6 ± 14.9 years, 69 % male) were more likely than controls (n = 663, 66.2 ± 11.6 years, 67 % male) to have diabetes (40 vs 32 %; p < 0.01), left ventricular ejection

fraction (LVEF) $\leq 35\%$ (27 vs 11 %; $p < 0.01$), prolonged QTc (≥ 450 ms; 54 vs 28 %; $p < 0.01$) and positive (19 vs 13 %; $p < 0.01$) or flat T wave (14 vs 7 %; $p < 0.01$) in aVR. On multivariable analysis, a positive/flat T wave in aVR was independently associated with SCD (OR 1.9, 95 % CI 1.3–2.8, $p < 0.01$). However, a positive T wave alone lost statistical significance in patients with LVEF $\leq 35\%$ and QTc ≥ 450 ms. In a subgroup analysis among patients with normal LVEF, QTc, and no diabetes, a positive T wave in aVR (but not a flat T wave) remained associated with SCD (OR 2.8, 95 % CI 1.2–6.1, $p < 0.01$). Conclusions: A positive or flat T wave in lead aVR was associated with SCD in subsets of patients. This simple ECG marker in this often-ignored lead may contribute to enhancement of SCD risk stratification, and warrants further evaluation. © 2015, Springer Science+Business Media New York.

Phillips, T. J., Mootz, J. R. K., & Reed, C. (2016). *Identification of treatment targets in a genetic mouse model of voluntary methamphetamine drinking* Academic Press Inc.

Methamphetamine has powerful stimulant and euphoric effects that are experienced as rewarding and encourage use. Methamphetamine addiction is associated with debilitating illnesses, destroyed relationships, child neglect, violence, and crime; but after many years of research, broadly effective medications have not been identified. Individual differences that may impact not only risk for developing a methamphetamine use disorder but also affect treatment response have not been fully considered. Human studies have identified candidate genes that may be relevant, but lack of control over drug history, the common use or coabuse of multiple addictive drugs, and restrictions on the types of data that can be collected in humans are barriers to progress. To overcome some of these issues, a genetic animal model comprised of lines of mice selectively bred for high and low voluntary methamphetamine intake was developed to identify risk and protective alleles for methamphetamine consumption, and identify therapeutic targets. The mu opioid receptor gene was supported as a target for genes within a top-ranked transcription factor network associated with level of methamphetamine intake. In addition, mice that consume high levels of methamphetamine were found to possess a nonfunctional form of the trace amine-associated receptor 1 (TAAR1). The Taar1 gene is within a mouse chromosome 10 quantitative trait locus for methamphetamine consumption, and TAAR1 function determines sensitivity to aversive effects of methamphetamine that may curb intake. The genes, gene

interaction partners, and protein products identified in this genetic mouse model represent treatment target candidates for methamphetamine addiction. © 2016 Elsevier Inc.

Piantino, J. A. (2015). Timing of anticonvulsant administration in status epilepticus. *Pediatric Neurology Briefs*, 29(6), 43-29-6-2.

Investigators from the Pediatric Status Epilepticus Research Group studied the time elapsed from onset of pediatric convulsive status epilepticus (SE) to administration of antiepileptic drugs (AED).

Pohl, K. M., Sullivan, E. V., Rohlfing, T., Chu, W., Kwon, D., Nichols, B. N., et al. (2016). Harmonizing DTI measurements across scanners to examine the development of white matter microstructure in 803 adolescents of the NCANDA study. *Neuroimage*, 130, 194-213.

Neurodevelopment continues through adolescence, with notable maturation of white matter tracts comprising regional fiber systems progressing at different rates. To identify factors that could contribute to regional differences in white matter microstructure development, large samples of youth spanning adolescence to young adulthood are essential to parse these factors. Recruitment of adequate samples generally relies on multi-site consortia but comes with the challenge of merging data acquired on different platforms. In the current study, diffusion tensor imaging (DTI) data were acquired on GE and Siemens systems through the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), a multi-site study designed to track the trajectories of regional brain development during a time of high risk for initiating alcohol consumption. This cross-sectional analysis reports baseline Tract-Based Spatial Statistic (TBSS) of regional fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (L1), and radial diffusivity (LT) from the five consortium sites on 671 adolescents who met no/low alcohol or drug consumption criteria and 132 adolescents with a history of exceeding consumption criteria. Harmonization of DTI metrics across manufacturers entailed the use of human-phantom data, acquired multiple times on each of three non-NCANDA participants at each site's MR system, to determine a manufacturer-specific correction factor. Application of the correction factor derived from human phantom data measured on MR systems from different manufacturers reduced the standard deviation of the DTI metrics for FA by almost a half, enabling harmonization of data that

would have otherwise carried systematic error. Permutation testing supported the hypothesis of higher FA and lower diffusivity measures in older adolescents and indicated that, overall, the FA, MD, and L1 of the boys were higher than those of the girls, suggesting continued microstructural development notable in the boys. The contribution of demographic and clinical differences to DTI metrics was assessed with General Additive Models (GAM) testing for age, sex, and ethnicity differences in regional skeleton mean values. The results supported the primary study hypothesis that FA skeleton mean values in the no/low-drinking group were highest at different ages. When differences in intracranial volume were covaried, FA skeleton mean reached a maximum at younger ages in girls than boys and varied in magnitude with ethnicity. Our results, however, did not support the hypothesis that youth who exceeded exposure criteria would have lower FA or higher diffusivity measures than the no/low-drinking group; detecting the effects of excessive alcohol consumption during adolescence on DTI metrics may require longitudinal study. © 2016 Elsevier Inc.

Porter, A. C., Triebwasser, J. E., Tuuli, M., Caughey, A. B., Macones, G. A., & Cahill, A. G. (2015). Fetal sex differences in intrapartum electronic fetal monitoring. *American Journal of Perinatology*, Objective The article aimed to estimate differences in electronic fetal monitoring (EFM) patterns in term gestations attributable to fetal sex. Study Design We conducted a prospective cohort study of consecutive, singleton, nonanomalous, term gestations that labored during admission. EFM characteristics in the 30 minutes prior to delivery were evaluated. Logistic regression models estimated adjusted risks for EFM features by sex. To further estimate the impact of sex, we limited the analysis to gestations without composite morbidity (morbidity defined as arterial cord pH <7.20, 5-minute Apgar <7, or neonatal intensive care unit admission). Results Of 2,639 deliveries, 1,400 (53%) were male. Male fetuses had a higher number of decelerations (median [interquartile range]: 8 [5, 11] vs. 7 [4, 10], $p < 0.003$) and increased total deceleration area (adjusted odds ratio [aOR]: 1.11, 95% confidence interval [CI] :1.04, 1.18). Male fetuses were at increased risk for prolonged decelerations (aOR: 1.21, 95% CI: 1.03, 1.42) and repetitive variable decelerations (aOR: 1.24, 95% CI: 1.05, 1.47). Among neonates without composite morbidity ($n = 2,446$, 92.7%), male sex conferred an increased risk of late decelerations (aOR: 1.21, 95% CI: 1.02, 1.43) and increased total deceleration area (aOR: 1.12, 95% CI: 1.05,

1.20). Conclusion There are significant sex differences in EFM patterns at term among pregnancies without evidence of acidemia. This suggests that interpretation of EFM patterns may need to take into account factors such as fetal sex. Copyright © 2015, Thieme Medical Publishers. All rights reserved.

Prasad, V., Fojo, T., & Brada, M. (2016). Precision oncology: Origins, optimism, and potential. *The Lancet Oncology*, 17(2), e81-e86.

Imatinib, the first and arguably the best targeted therapy, became the springboard for developing drugs aimed at molecular targets deemed crucial to tumours. As this development unfolded, a revolution in the speed and cost of genetic sequencing occurred. The result—an armamentarium of drugs and an array of molecular targets—set the stage for precision oncology, a hypothesis that cancer treatment could be markedly improved if therapies were guided by a tumour's genomic alterations. Drawing lessons from the biological basis of cancer and recent empirical investigations, we take a more measured view of precision oncology's promise. Ultimately, the promise is not our concern, but the threshold at which we declare success. We review reports of precision oncology alongside those of precision diagnostics and novel radiotherapy approaches. Although confirmatory evidence is scarce, these interventions have been widely endorsed. We conclude that the current path will probably not be successful or, at a minimum, will have to undergo substantive adjustments before it can be successful. For the sake of patients with cancer, we hope one form of precision oncology will deliver on its promise. However, until confirmatory studies are completed, precision oncology remains unproven, and as such, a hypothesis in need of rigorous testing. © 2016 Elsevier Ltd.

Prasad, V. K. (2016). Vinay prasad on the use of exaggerated language in cancer research, and how it can mislead doctors, patients, and the public. *ONCOLOGY (United States)*, 30(2)

Rabbitts, J. A., Holley, A. L., Groenewald, C. B., & Palermo, T. M. (2016). Association between widespread pain scores and functional impairment and health-related quality of life in clinical samples of children. *The Journal of Pain : Official Journal of the American Pain Society*, Pain involving several body regions generally represents nervous system pathophysiology shifting from predominantly peripheral to more central. In adults, higher widespread pain scores are

clinically meaningful and confer risk for poor response to treatment. It is unknown whether widespread pain is similarly important in children. To address this gap, we conducted an observational study examining (1) associations between widespread pain and functional impairment and health-related quality of life (HRQOL) in clinical pediatric samples, and (2) associations among sociodemographic factors and pain catastrophizing with widespread pain scores. Participants were 166 children age 10-18 years from three samples (acute pain, pre-surgery, chronic pain). Children self-reported pain intensity, pain catastrophizing, functional impairment and HRQOL. Children indicated pain locations on a body diagram, which was coded using the American College of Rheumatology definition of widespread pain. Results revealed higher widespread pain scores were associated with greater functional impairment with routine activities ($F=3.15$, $p=0.02$) and poorer HRQOL ($F=3.29$, $p=0.02$), adjusting for pain intensity, study group and demographics. Older age ($B=0.11$, $p=0.01$), and Hispanic ethnicity ($B=0.67$, $p=.03$) were associated with higher widespread pain scores. Findings support incorporating evaluation of widespread pain into pediatric pain assessment. Future research is needed to examine longitudinal impact of widespread pain on children's treatment outcomes. PERSPECTIVE: This article examines the association between widespread pain scores and functional impairment and HRQOL in community and clinical samples of children. Assessment of the spatial distribution of the pain experience provides unique information that may identify children at risk for poorer health.

Ran, R., Kuang, P., & Mah, N. D. (2016). Rapid ventricular response or tachycardia? the three faces of atrial fibrillation. *American Journal of Emergency Medicine*,

Reinhart, P. N., Souza, P. E., Srinivasan, N. K., & Gallun, F. J. (2016). Effects of reverberation and compression on consonant identification in individuals with hearing impairment. *Ear and Hearing*, 37(2), 144-152.

Objectives: Hearing aids are frequently used in reverberant environments; however, relatively little is known about how reverberation affects the processing of signals by modern hearing-aid algorithms. The purpose of this study was to investigate the acoustic and behavioral effects of reverberation and wide-dynamic range compression (WDRC) in hearing aids on consonant

identification for individuals with hearing impairment. Design: Twenty-three listeners with mild to moderate sloping sensorineural hearing loss were tested monaurally under varying degrees of reverberation and WDRC conditions. Listeners identified consonants embedded within vowel-consonant-vowel nonsense syllables. Stimuli were processed to simulate a range of realistic reverberation times and WDRC release times using virtual acoustic simulations. In addition, the effects of these processing conditions were acoustically analyzed using a model of envelope distortion to examine the effects on the temporal envelope. Results: Aided consonant identification significantly decreased as reverberation time increased. Consonant identification was also significantly affected by WDRC release time. This relationship was such that individuals tended to perform significantly better with longer release times. There was no significant interaction between reverberation and WDRC. The application of the acoustic model to the processed signal showed a close relationship between trends in the behavioral performance and distortion to the temporal envelope resulting from reverberation and WDRC. The results of the acoustic model demonstrated the same trends found in the behavioral data for both reverberation and WDRC. Conclusions: Reverberation and WDRC release time both affect aided consonant identification for individuals with hearing impairment, and these condition effects are associated with alterations to the temporal envelope. There was no significant interaction between reverberation and WDRC release time. Copyright © 2015 Wolters Kluwer Health, Inc.

Renée Umstattd Meyer, M., Perry, C. K., Sumrall, J. C., Patterson, M. S., Walsh, S. M., Clendennen, S. C., et al. (2016). Physical activity-related policy and environmental strategies to prevent obesity in rural communities: A systematic review of the literature, 2002-2013. *Preventing Chronic Disease, 13*(1)

Introduction: Health disparities exist between rural and urban residents; in particular, rural residents have higher rates of chronic diseases and obesity. Evidence supports the effectiveness of policy and environmental strategies to prevent obesity and promote health equity. In 2009, the Centers for Disease Control and Prevention recommended 24 policy and environmental strategies for use by local communities: the Common Community Measures for Obesity Prevention (COCOMO); 12 strategies focus on physical activity. This review was conducted to synthesize evidence on the implementation, relevance, and effectiveness of physical activity-

related policy and environmental strategies for obesity prevention in rural communities. Methods: A literature search was conducted in PubMed, PsycINFO, Web of Science, CINHAL, and PAIS databases for articles published from 2002 through May 2013 that reported findings from physical activity-related policy or environmental interventions conducted in the United States or Canada. Each article was extracted independently by 2 researchers. Results: Of 2,002 articles, 30 articles representing 26 distinct studies met inclusion criteria. Schools were the most common setting (n = 18 studies). COCOMO strategies were applied in rural communities in 22 studies; the 2 most common COCOMO strategies were "enhance infrastructure supporting walking" (n = 11) and "increase opportunities for extracurricular physical activity" (n = 9). Most studies (n = 21) applied at least one of 8 non-COCOMO strategies; the most common was increasing physical activity opportunities at school outside of physical education (n = 8). Only 14 studies measured or reported physical activity outcomes (10 studies solely used self-report); 10 reported positive changes. Conclusion: Seven of the 12 COCOMO physical activity-related strategies were successfully implemented in 2 or more studies, suggesting that these 7 strategies are relevant in rural communities and the other 5 might be less applicable in rural communities. Further research using robust study designs and measurement is needed to better ascertain implementation success and effectiveness of COCOMO and non-COCOMO strategies in rural communities.

Roberts, C. C., Kransdorf, M. J., Beaman, F. D., Adler, R. S., Amini, B., Appel, M., et al. (2016). ACR appropriateness criteria follow-up of malignant or aggressive musculoskeletal tumors. *Journal of the American College of Radiology : JACR*,
Appropriate imaging modalities for the follow-up of malignant or aggressive musculoskeletal tumors include radiography, MRI, CT, 18F-2-fluoro-2-deoxy-D-glucose PET/CT, 99mTc bone scan, and ultrasound. Clinical scenarios reviewed include evaluation for metastatic disease to the lung in low- and high-risk patients, for osseous metastatic disease in asymptomatic and symptomatic patients, for local recurrence of osseous tumors with and without significant hardware present, and for local recurrence of soft tissue tumors. The timing for follow-up of pulmonary metastasis surveillance is also reviewed. The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every three years by a multidisciplinary expert panel.

The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Roberts, V. H., Lo, J. O., Salati, J. A., Lewandowski, K. S., Lindner, J. R., Morgan, T. K., et al. (2016).

Quantitative assessment of placental perfusion by contrast-enhanced ultrasound in macaques and human subjects. *American Journal of Obstetrics and Gynecology*, 214(3), 369.e1-369.e8.

BACKGROUND: The uteroplacental vascular supply is a critical determinant of placental function and fetal growth. Current methods for the in vivo assessment of placental blood flow are limited.

OBJECTIVE: We demonstrate the feasibility of the use of contrast-enhanced ultrasound imaging to visualize and quantify perfusion kinetics in the intervillous space of the primate placenta.

STUDY DESIGN: Pregnant Japanese macaques were studied at mid second trimester and in the early third trimester. Markers of injury were assessed in placenta samples from animals with or without contrast-enhanced ultrasound exposure (n = 6/group). Human subjects were recruited immediately before scheduled first-trimester pregnancy termination. All studies were performed with maternal intravenous infusion of lipid-shelled octofluoropropane microbubbles with image acquisition with a multipulse contrast-specific algorithm with destruction-replenishment analysis of signal intensity for assessment of perfusion. RESULTS: In macaques, the rate of perfusion in the intervillous space was increased with advancing gestation. No evidence of microvascular hemorrhage or acute inflammation was found in placental villous tissue and expression levels of caspase-3, nitrotyrosine and heat shock protein 70 as markers of apoptosis, nitrative, and oxidative stress, respectively, were unchanged by contrast-enhanced ultrasound exposure. In humans, placental perfusion was visualized at 11 weeks gestation, and preliminary data reveal regional differences in intervillous space perfusion within an individual placenta. By electron microscopy, we demonstrate no evidence of ultrastructure damage to the microvilli on the syncytiotrophoblast after first-trimester ultrasound studies. CONCLUSIONS: Use of contrast-enhanced ultrasound did not result in placental structural damage and was able to identify intervillous space perfusion rate differences within a placenta. Contrast-enhanced ultrasound

imaging may offer a safe clinical tool for the identification of pregnancies that are at risk for vascular insufficiency; early recognition may facilitate intervention and improved pregnancy outcomes.

Roselli, C. E., Meaker, M., Stormshak, F., & Estill, C. T. (2016). Effects of long-term flutamide treatment during development on sexual behavior and hormone responsiveness in rams. *Journal of Neuroendocrinology*,

Testosterone (T) exposure during midgestation differentiates neural circuits controlling sex-specific behaviors and patterns of gonadotropin secretion in male sheep. T acts through androgen receptors (AR) and/or after aromatization to estradiol and binding to estrogen receptors. The current study assessed the role of AR activation in male sexual differentiation. We compared rams that were exposed to the AR antagonist flutamide (Flu) throughout the critical period (i.e. day 30 - 90 of gestation) to control rams and ewes that received no prenatal treatments. The external genitalia of all Flu rams were phenotypically female. Testes were positioned subcutaneously in the inguinal region of the abdomen, exhibited seasonally impaired androgen secretion and were azospermic. Flu rams displayed male-typical precopulatory and mounting behaviors, but could not intromit or ejaculate because they lacked a penis. Flu rams exhibited greater mounting behavior than control rams, and like controls, showed sexual partner preferences for estrous ewes. Neither control nor Flu rams responded to estradiol treatments with displays of female-typical receptive behavior or LH surge responses; whereas all control ewes responded as expected. The ovine sexually dimorphic nucleus in Flu rams was intermediate in volume between control rams and ewes and significantly different from both.. These results indicate that prenatal antiandrogen exposure is not able to block male sexual differentiation in sheep and suggest that compensatory mechanisms intervene to maintain sufficient androgen stimulation during development. This article is protected by copyright. All rights reserved.

Rosenbaum, J. T., Lin, P., & Asquith, M. (2016). Does the microbiome cause B27-related acute anterior uveitis? *Ocular Immunology and Inflammation*, , 1-5.

The microbiome is strongly implicated in a broad spectrum of immune-mediated diseases. Data support the concept that HLA molecules shape the microbiome. We provide hypotheses to

reconcile how HLA-B27 might affect the microbiome and in turn predispose to acute anterior uveitis. These theories include bacterial translocation, antigenic mimicry, and dysbiosis leading to alterations in regulatory and effector T-cell subsets.

Rosenbaum, J. T., Rosenzweig, H. L., & Martin, T. M. (2016). Blau syndrome. (pp. 881-883) Springer Berlin Heidelberg.

Blau syndrome is an autosomal dominant disease which characteristically results in a granulomatous rash, arthritis, and uveitis. Blau syndrome was first described in 1985 in two separate reports. Although the description by Jabs and colleagues appeared first, the eponym, Blau, is widely applied to this syndrome. Many prefer the term, pediatric granulomatous arthritis and uveitis to the name, Blau [15]. © Springer-Verlag Berlin Heidelberg 2016.

Rosenbaum, J. T., Sibley, C. H., & Lin, P. (2016). Retinal vasculitis. *Current Opinion in Rheumatology*, 28(3), 228-235.

PURPOSE OF REVIEW: Ophthalmologists and rheumatologists frequently have a miscommunication among themselves, and as a result differ in their opinion for patients consulting them with retinal vasculitis. This report seeks to establish a common understanding of the term, retinal vasculitis, and to review recent studies on this diagnosis. RECENT FINDINGS: The genetic basis of some rare forms of retinal vascular disease has recently been described. Identified genes include CAPN5, TREX1, and TNFAIP3; Behcet's disease is a systemic illness that is very commonly associated with occlusive retinal vasculitis; retinal imaging, including fluorescein angiography and other newer imaging modalities, has proven crucial to the identification and characterization of retinal vasculitis and its complications; although monoclonal antibodies to interleukin-17A or interleukin-1 beta failed in trials for Behcet's disease, antibodies to TNF-alpha, either infliximab or adalimumab, have demonstrated consistent benefit in managing this disease. Interferon treatment and B-cell depletion therapy via rituximab may be beneficial in certain types of retinal vasculitis. SUMMARY: Retinal vasculitis is an important entity for rheumatologists to understand. Retinal vasculitis associated with Behcet's disease responds to monoclonal antibodies that neutralize TNF, but the many other forms of noninfectious retinal vasculitis may require alternate therapeutic management.

Ross, D. A. (2016). Letter to the editor: Steroid use in anterior cervical discectomy and fusion. *Journal of Neurosurgery.Spine*, , 1-2.

Rozner, M. A., Schultheis, L., & Schulman, P. M. (2016). The unstated murphy's law of the operating room: If something goes wrong, blame anesthesia. *A & A Case Reports*, 6(6), 139-141.

Rudmik, L., Soler, Z. M., Hopkins, C., Schlosser, R. J., Peters, A., White, A. A., et al. (2016). Defining appropriateness criteria for endoscopic sinus surgery during management of uncomplicated adult chronic rhinosinusitis: A RAND/UCLA appropriateness study. *Rhinology*,

INTRODUCTION: Appropriate indications for endoscopic sinus surgery (ESS) for chronic rhinosinusitis (CRS) are currently poorly defined. The lack of clear surgical indications for ESS likely contributes to the large geographic variation in surgical rates and contributes to reduced quality of care. The objective of this study was to define appropriateness criteria for ESS during management of adult patients with uncomplicated CRS. METHODS: The RAND/UCLA appropriateness methodology was performed. An international, multi-disciplinary panel of 10 experts in CRS was formed and completed two rounds of a modified Delphi ranking process along with a face-to-face meeting. RESULTS: A total of 624 clinical scenarios were ranked, 312 scenarios each for CRS with and CRS without nasal polyps. For adult patients with uncomplicated CRS with nasal polyps, ESS can be appropriately offered when the CT Lund-Mackay score is equals or is greater than 1 and there has been a minimum trial of a topical intranasal corticosteroid plus a short-course of systemic corticosteroid with a post-treatment total SNOT-22 score equals or is greater than 20. For adult patients with uncomplicated CRS without nasal polyps, ESS can be appropriately offered when the CT Lund-Mackay score is equals or is greater than 1 and there has been a minimum trial of a topical intranasal corticosteroid plus either a short-course of a broad spectrum/culture-directed systemic antibiotic or the use of a prolonged course of systemic low-dose anti-inflammatory antibiotic with a post-treatment total SNOT-22 score equals or is greater than 20. CONCLUSION: This study has developed and reported of list of appropriateness criteria to offer ESS as a treatment option during management of uncomplicated adult CRS. The extent or technique of ESS was not addressed in this study and will depend on surgeon and patient factors. Furthermore, these criteria are the minimal threshold to make ESS a

treatment option and do not imply that all patients meeting these criteria require surgery. The decision to perform ESS should be made after an informed patient makes a preference-sensitive decision to proceed with surgery. Applying these appropriateness criteria for ESS may optimize patient selection, reduce the incidence of unwarranted surgery, and assist clinicians in providing high quality, patient-centered care to patients with CRS.

Ruhland, M. K., Coussens, L. M., & Stewart, S. A. (2016). Senescence and cancer: An evolving inflammatory paradox. *Biochimica Et Biophysica Acta - Reviews on Cancer*, 1865(1), 14-22.

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

Ruiz de Gauna, S., Gonzalez-Otero, D. M., Ruiz, J., & Russell, J. K. (2016). Feedback on the rate and depth of chest compressions during cardiopulmonary resuscitation using only accelerometers. *PloS One*, 11(3), e0150139.

BACKGROUND: Quality of cardiopulmonary resuscitation (CPR) is key to increase survival from cardiac arrest. Providing chest compressions with adequate rate and depth is difficult even for

well-trained rescuers. The use of real-time feedback devices is intended to contribute to enhance chest compression quality. These devices are typically based on the double integration of the acceleration to obtain the chest displacement during compressions. The integration process is inherently unstable and leads to important errors unless boundary conditions are applied for each compression cycle. Commercial solutions use additional reference signals to establish these conditions, requiring additional sensors. Our aim was to study the accuracy of three methods based solely on the acceleration signal to provide feedback on the compression rate and depth.

MATERIALS AND METHODS: We simulated a CPR scenario with several volunteers grouped in couples providing chest compressions on a resuscitation manikin. Different target rates (80, 100, 120, and 140 compressions per minute) and a target depth of at least 50 mm were indicated. The manikin was equipped with a displacement sensor. The accelerometer was placed between the rescuer's hands and the manikin's chest. We designed three alternatives to direct integration based on different principles (linear filtering, analysis of velocity, and spectral analysis of acceleration). We evaluated their accuracy by comparing the estimated depth and rate with the values obtained from the reference displacement sensor. **RESULTS:** The median (IQR) percent error was 5.9% (2.8-10.3), 6.3% (2.9-11.3), and 2.5% (1.2-4.4) for depth and 1.7% (0.0-2.3), 0.0% (0.0-2.0), and 0.9% (0.4-1.6) for rate, respectively. Depth accuracy depended on the target rate ($p < 0.001$) and on the rescuer couple ($p < 0.001$) within each method.

CONCLUSIONS: Accurate feedback on chest compression depth and rate during CPR is possible using exclusively the chest acceleration signal. The algorithm based on spectral analysis showed the best performance. Despite these encouraging results, further research should be conducted to assess the performance of these algorithms with clinical data.

Ruszczyc, M., Zirpoli, G., Kumar, S., Bandera, E. V., Bovbjerg, D. H., Jandorf, L., et al. (2016). Breast cancer risk factor associations differ for pure versus invasive carcinoma with an in situ component in case-control and case-case analyses. *Cancer Causes and Control*, 27(2), 183-198.

Purpose: Invasive ductal carcinoma (IDC) is diagnosed with or without a ductal carcinoma in situ (DCIS) component. Previous analyses have found significant differences in tumor characteristics between pure IDC lacking DCIS and mixed IDC with DCIS. We will test our hypothesis that pure IDC represents a form of breast cancer with etiology and risk factors distinct from mixed

IDC/DCIS. Methods: We compared reproductive risk factors for breast cancer risk, as well as family and smoking history between 831 women with mixed IDC/DCIS (n = 650) or pure IDC (n = 181), and 1,620 controls, in the context of the Women's Circle of Health Study (WCHS), a case-control study of breast cancer in African-American and European-American women. Data on reproductive and lifestyle factors were collected during interviews, and tumor characteristics were abstracted from pathology reports. Case-control and case-case analyses were conducted using unconditional logistic regression. Results: Most risk factors were similarly associated with pure IDC and mixed IDC/DCIS. However, among postmenopausal women, risk of pure IDC was lower in women with body mass index (BMI) 25 to <30 [odds ratio (OR) 0.66; 95 % confidence interval (CI) 0.35-1.23] and BMI \geq 30 (OR 0.33; 95 % CI 0.18-0.67) compared to women with BMI < 25, with no associations with mixed IDC/DCIS. In case-case analyses, women who breastfed up to 12 months (OR 0.55; 95 % CI 0.32-0.94) or longer (OR 0.47; 95 % CI 0.26-0.87) showed decreased odds of pure IDC than mixed IDC/DCIS compared to those who did not breastfeed. Conclusions: Associations with some breast cancer risk factors differed between mixed IDC/DCIS and pure IDC, potentially suggesting differential developmental pathways. These findings, if confirmed in a larger study, will provide a better understanding of the developmental patterns of breast cancer and the influence of modifiable risk factors, which in turn could lead to better preventive measures for pure IDC, which have worse disease prognosis compared to mixed IDC/DCIS. © 2015, Springer International Publishing Switzerland.

Ryabinin, A. E., & Hostetler, C. M. (2016). *Prairie voles as a model to screen medications for the treatment of alcoholism and addictions* Academic Press Inc.

Most preclinical studies of medications to treat addictions are performed in mice and rats. These two rodent species belong to one phylogenetic subfamily, which narrows the likelihood of identifying potential mechanisms regulating addictions in other species, ie, humans. Expanding the genetic diversity of organisms modeling alcohol and drug abuse enhances our ability to screen for medications to treat addiction. Recently, research laboratories adapted the prairie vole model to study mechanisms of alcohol and drugs of abuse. This development not only expanded the diversity of genotypes used to screen medications, but also enhanced capabilities of such screens. Prairie voles belong to 3-5% of mammalian species exhibiting social monogamy. This

unusual trait is reflected in their ability to form lasting long-term affiliations between adult individuals. The prairie vole animal model has high predictive validity for mechanisms regulating human social behaviors. In addition, these animals exhibit high alcohol intake and preference. In laboratory settings, prairie voles are used to model social influences on drug reward and alcohol consumption as well as effects of addictive substances on social bonding. As a result, this species can be adapted to screen medications whose effectiveness could be (a) resistant to social influences promoting excessive drug taking, (b) dependent on the presence of social support, and (c) medications affecting harmful social consequences of alcohol and drug abuse. This report reviews the literature on studies of alcohol and psychostimulants in prairie voles and discusses capabilities of this animal model as a screen for novel medications to treat alcoholism and addictions. © 2016 Elsevier Inc.

Saade, G. R., Boggess, K. A., Sullivan, S. A., Markenson, G. R., Iams, J. D., Coonrod, D. V., et al. (2016). Development and validation of a spontaneous preterm delivery predictor in asymptomatic women. *American Journal of Obstetrics and Gynecology*,
Background: Preterm delivery remains the leading cause of perinatal mortality. Risk factors and biomarkers have traditionally failed to identify the majority of preterm deliveries. Objective: To develop and validate a mass spectrometry-based serum test to predict spontaneous preterm delivery in asymptomatic pregnant women. Study Design: A total of 5501 pregnant women were enrolled between 170/7 and 286/7 weeks gestational age in the prospective Proteomic Assessment of Preterm Risk study at 11 sites in the United States between 2011 and 2013. Maternal blood was collected at enrollment and outcomes collected following delivery. Maternal serum was processed by a proteomic workflow, and proteins were quantified by multiple reaction monitoring mass spectrometry. The discovery and verification process identified 2 serum proteins, insulin-like growth factor-binding protein 4 (IBP4) and sex hormone-binding globulin (SHBG), as predictors of spontaneous preterm delivery. We evaluated a predictor using the log ratio of the measures of IBP4 and SHBG (IBP4/SHBG) in a clinical validation study to classify spontaneous preterm delivery cases (<370/7 weeks gestational age) in a nested case-control cohort different from subjects used in discovery and verification. Strict blinding and independent statistical analyses were employed. Results: The predictor had an area under the receiver

operating characteristic curve value of 0.75 and sensitivity and specificity of 0.75 and 0.74, respectively. The IBP4/SHBG predictor at this sensitivity and specificity had an odds ratio of 5.04 for spontaneous preterm delivery. Accuracy of the IBP4/SHBG predictor increased using earlier case-vs-control gestational age cutoffs (eg, <350/7 vs ≥350/7 weeks gestational age). Importantly, higher-risk subjects defined by the IBP4/SHBG predictor score generally gave birth earlier than lower-risk subjects. Conclusion: A serum-based molecular predictor identifies asymptomatic pregnant women at risk of spontaneous preterm delivery, which may provide utility in identifying women at risk at an early stage of pregnancy to allow for clinical intervention. This early detection would guide enhanced levels of care and accelerate development of clinical strategies to prevent preterm delivery. © 2016 The Authors.

Sakuraba, A., Armuzzi, A., Keyashian, K., & Naganuma, M. (2016). Novel topics in inflammatory bowel disease. *BioMed Research International*, 2016, 8958751.

Salehi, S., Cooper, P., Smith, A., & Ferracane, J. (2016). Dentin matrix components extracted with phosphoric acid enhance cell proliferation and mineralization. *Dental Materials*, 32(3), 334-342. Objective Acids, such as those used in adhesive dentistry, have been shown to solubilize bioactive molecules from dentin. These dentin matrix components (DMC) may promote cell proliferation and differentiation, and ultimately contribute to dentin regeneration. The objective of this study was to evaluate the potential for varying concentrations of DMC extracted from human dentin by phosphoric acid of a range of pHs to stimulate proliferation and mineralization of two different cultured pulp cell populations. Methods DMC were solubilized from powdered human dentin (7 days - 4 °C) by phosphoric acid of pH 1, 3, and 5 and also, EDTA. Extracts were dialyzed for 7 days against distilled water and lyophilized. Undifferentiated mouse dental pulp cells (OD-21) and cells of the odontoblast-like cell line (MDPC-23) were seeded in six-well plates (1×10^5) and cultured for 24 h in DMEM (Dulbecco's modified Eagle's medium) containing 10% (v/v) FBS (fetal bovine serum). The cells were washed with serum-free medium and then treated with different concentrations of DMC (0.01, 0.1, 1.0 and 10.0 µg/ml) daily in serum free medium for 7 days. After 3, 5 (MDPC-23 only), and 7 days of treatment, cell proliferation was measured using 10 vol% Alamar blue solution, which was added to each well for 1 h. Cell numbers were

first measured by cell counting (Trypan blue; n = 5) and Alamar blue fluorescence to validate the assay, which was then used for the subsequent assessments of proliferation. Mineralization was assessed by Alizarin Red S assay after 12 days exposure to DMC (n = 5). Controls were media-only (DMEM) and dexamethasone (DEX; positive control). Results were analysed by ANOVA/Tukey's ($p \leq 0.05$). Results There was a linear correlation between cell counts and Alamar blue fluorescence ($R^2 > 0.96$ for both cell types), verifying the validity of the Alamar blue assay for these cell types. In general, there was a dose-dependent trend for enhanced cell proliferation with higher concentration of DMC for both cell lines, especially at 10.0 $\mu\text{g/ml}$. DEX exposure resulted in significantly higher mineralization, but did not affect cell proliferation. DMC exposure demonstrated significantly greater mineralization than media-only control for 10 $\mu\text{g/ml}$ for all extracts, and at lower concentrations for EDTA and pH 5 extracts. Significance Human dentin matrix components solubilized by acids at pH levels found in commercial dentin adhesives enhanced cell proliferation and mineralization of mouse and rat undifferentiated dental pulp cells when presented in adequate concentration. © 2015 Academy of Dental Materials.

Salinsky, M., Parko, K., Rutecki, P., Boudreau, E., & Storzbach, D. (2016). Attributing seizures to TBI: Validation of a brief patient questionnaire. *Epilepsy & Behavior : E&B*, 57(Pt A), 141-144.

PURPOSE: Traumatic brain injury (TBI) is an important cause of epilepsy and has also been associated with psychogenic nonepileptic seizures (PNES). We designed a brief questionnaire assessing patient beliefs regarding TBI as the cause of their seizures (Patient Seizure Etiology Questionnaire; PSEQ). This study reports content validity for the PSEQ. METHODS: Ninety Veterans undergoing comprehensive evaluation at 3 VA epilepsy centers completed the PSEQ, a series of questions regarding possible causes for their seizures, including TBI. The PSEQ was scored as YES vs. NO for TBI as the proposed cause of seizures. For each patient, two expert reviewers independently completed a structured chart review to determine whether TBI was the proposed cause of seizures (n=180 reviews). Kappa statistic was used to assess agreement between the PSEQ and each chart review and between the PSEQ and combined chart reviews where both reviewers agreed on a TBI seizure etiology. RESULTS: The PSEQ scored higher overall rates for a TBI seizure etiology than did expert chart reviews (40% vs. 28%; $p < 0.001$). The PSEQ agreed with 82% of 180 independent chart reviews (sensitivity 88%; specificity 79%).

Kappa statistic for agreement was 0.60. The two reviewers agreed on a probable TBI seizure etiology for 83% of chart reviews. The PSEQ sensitivity increased to 100% when both reviewers were in agreement. CONCLUSION: The PSEQ provides a direct, standardized measure of patient beliefs regarding TBI as the cause of their seizures and has moderate-substantial agreement with expert chart reviews.

Salvador, J. G., Devargas, E. C., & Feldstein Ewing, S. W. (2015). Who are hispanic youth?

considerations for adolescent addiction clinical research and treatment. *Alcoholism Treatment Quarterly*, 33(3), 348-362.

Despite a strong and growing presence within the United States, there is a history of health disparities for Hispanic populations. These issues have been even more pronounced for Hispanic youth. To take a step towards providing culturally relevant care for Hispanic youth, this article presents an overview of important issues for clinical treatment and research including Hispanic cultural heritage, Hispanic identity, and biculturalism/multiculturalism. Furthermore, this review discusses salient factors for Hispanic youth including acculturation, cultural norms and cultural scripts. Understanding these factors in relation to substance abuse treatment is critical to offering the best services for Hispanic youth. Copyright © 2015 Taylor & Francis.

Samorano, L. P., Hanifin, J. M., Simpson, E. L., & Leshem, Y. A. (2016). Inadequate response to

ustekinumab in atopic dermatitis - A report of two patients. *Journal of the European Academy of Dermatology and Venereology*, 30(3), 522-523.

Sandsmark, D. K., Kumar, M. A., Woodward, C. S., Schmitt, S. E., Park, S., & Lim, M. M. (2016).

Sleep features on continuous electroencephalography predict rehabilitation outcomes after severe traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, 31(2), 101-107.

OBJECTIVE: Sleep characteristics detected by electroencephalography (EEG) may be predictive of neurological recovery and rehabilitation outcomes after traumatic brain injury (TBI). We sought to determine whether sleep features were associated with greater access to rehabilitation therapies and better functional outcomes after severe TBI. METHODS: We retrospectively reviewed records of patients admitted with severe TBI who underwent 24 or more hours of continuous EEG (cEEG) monitoring within 14 days of injury for sleep elements and ictal activity.

Patient outcomes included discharge disposition and modified Rankin Scale (mRS). RESULTS: A total of 64 patients underwent cEEG monitoring for a mean of 50.6 hours. Status epilepticus or electrographic seizures detected by cEEG were associated with poor outcomes (death or discharge to skilled nursing facility). Sleep characteristics were present in 19 (30%) and associated with better outcome (89% discharged to home/acute rehabilitation; $P = .0002$). Lack of sleep elements on cEEG correlated with a poor outcome or mRS > 4 at hospital discharge ($P = .012$). Of those patients who were transferred to skilled nursing/acute rehabilitation, sleep architecture on cEEG associated with a shorter inpatient hospital stay (20 days vs 27 days) and earlier participation in therapy (9.8 days vs 13.2 days postinjury). Multivariable analyses indicated that sleep features on cEEG predicted functional outcomes independent of admission Glasgow Coma Scale and ictal-interictal activity. CONCLUSION: The presence of sleep features in the acute period after TBI indicates earlier participation in rehabilitative therapies and a better functional recovery. By contrast, status epilepticus, other ictal activity, or absent sleep architecture may portend a worse prognosis. Whether sleep elements detected by EEG predict long-term prognosis remains to be determined.

Sarai, M., Duszak, R., Jr, & Kaufman, J. A. (2016). Value-based medicine: Organizing IR care through integrated practice units. *Journal of Vascular and Interventional Radiology : JVIR*, 27(3), 336-338.

Sari, S., Dogu, F., Hwa, V., Haskologlu, S., Dauber, A., Rosenfeld, R., et al. (2016). A successful HSCT in a girl with novel LRBA mutation with refractory celiac disease. *Journal of Clinical Immunology*, 36(1), 8-11.

Saultz, J. (2016). Personal primary care. *Family Medicine*, 48(2), 89-90.

Saultz, J. (2016). Technology. *Family Medicine*, 48(1), 5-6.

Saultz, J. (2016). Unintended consequences. *Family Medicine*, 48(3), 173-174.

Schallhorn, J. M., Holiman, J. D., Stoeger, C. G., & Chamberlain, W. (2016). Quantification and patterns of endothelial cell loss due to eye bank preparation and injector method in descemet

membrane endothelial keratoplasty tissues. *Cornea*, 35(3), 377-382.

Purpose: To evaluate endothelial cell damage after eye bank preparation and passage through 1 of 2 different injectors for Descemet membrane endothelial keratoplasty grafts. Methods: Eighteen Descemet membrane endothelial keratoplasty grafts were prepared by Lions VisionGift with the standard partial prepeel technique and placement of an S-stamp for orientation. The grafts were randomly assigned to injection with either a glass- modified Jones tube injector (Gunther Weiss Scientific Glass) or a closed-system intraocular lens injector (Viscoject 2.2; Medical). After injection, the grafts were stained with the vital fluorescent dye C'alcein AM and digitally imaged. The percentage of cell loss was calculated by measuring the area of nonfluorescent pixels and dividing it by die total graft area pixels. Results: Grafts injected using the modified Jones tube injector had an overall cell loss of 27% \pm 5% [95% confidence interval, 21%- 35%]. Grafts injected using the closed-system intraocular lens injector had a cell loss of 32% \pm 8% (95% confidence interval, 21 %-45%). This difference was not statistically significant (P = 0.3). Several damage patterns including damage due to S-stamp placement were observed, but they did not correlate with injector type. Conclusions: In this in vitro study, there was no difference in the cell loss associated with the injector method. Grafts in both groups sustained significant cell loss and displayed evidence of graft preparation and S-stamp placement. Improvement in graft preparation and injection methods may improve cell retention. ©2016 Wolters Kluwer Health, Inc.

Schueler, M., Halbritter, J., Phelps, I. G., Braun, D. A., Otto, E. A., Porath, J. D., et al. (2016). Large-scale targeted sequencing comparison highlights extreme genetic heterogeneity in nephronophthisis-related ciliopathies. *Journal of Medical Genetics*, 53(3), 208-214.

Background: The term nephronophthisis-related ciliopathies (NPHP-RC) describes a group of rare autosomal-recessive cystic kidney diseases, characterised by broad genetic and clinical heterogeneity. NPHP-RC is frequently associated with extrarenal manifestations and accounts for the majority of genetically caused chronic kidney disease (CKD) during childhood and adolescence. Generation of a molecular diagnosis has been impaired by this broad genetic heterogeneity. However, recently developed high-throughput exon sequencing techniques represent powerful and efficient tools to screen large cohorts for dozens of causative genes.

Methods: Therefore, we performed massively multiplexed targeted sequencing using the modified molecular inversion probe strategy (MIPs) in an international cohort of 384 patients diagnosed with NPHP-RC. Results: As a result, we established the molecular diagnoses in 81/384 unrelated individuals (21.1%). We detected 127 likely disease-causing mutations in 18 of 34 evaluated NPHP-RC genes, 22 of which were novel. We further compared a subgroup of current findings to the results of a previous study in which we used an array-based microfluidic PCR technology in the same cohort. While 78 likely disease-causing mutations were previously detected by the array-based microfluidic PCR, the MIPs approach identified 94 likely pathogenic mutations. Compared with the previous approach, MIPs redetected 66 out of 78 variants and 28 previously unidentified variants, for a total of 94 variants. Conclusions: In summary, we demonstrate that the modified MIPs technology is a useful approach to screen large cohorts for a multitude of established NPHP genes in order to identify the underlying molecular cause. Combined application of two independent library preparation and sequencing techniques, however, may still be indicated for Mendelian diseases with extensive genetic heterogeneity in order to further increase diagnostic sensitivity.

Schuitevoerder, D., White, I., Fortino, J., & Vetto, J. (2016). Axillary web syndrome: An underappreciated complication of sentinel node biopsy in melanoma. *American Journal of Surgery*,

OBJECTIVE: Axillary web syndrome (AWS) is known to occur after axillary dissection and has been reported after axillary sentinel lymph node biopsy (ASLNB) for breast cancer. However, the incidence and outcomes of AWS after ASLNB for melanoma are unknown. METHODS: A retrospective review of prospectively collected, clinically node-negative patients undergoing ASLNB for melanoma at a single institution during a 14-year period was conducted to determine the incidence of AWS. Features pertaining to patients (age and gender), primary tumor (location, Breslow's depth), and nodes (number removed, positive node rate) were correlated with the occurrence of AWS. RESULTS: Of the 465 patients undergoing ASLNB, 21 (4.5%) developed AWS postoperatively. In comparison, the incidence of other complications in this population were infection 3%, bleeding 1.5%, wound dehiscence .8%, lymphocele 5%, and lymphedema .4%. There was no statistical difference between patients with or without AWS in terms of tumor

thickness, location of primary (upper extremity vs trunk), average number of sentinel nodes removed, positive SLNB rates (10% vs 12%), patient age, or gender. All cases of AWS resolved with expectant management; none required surgical intervention. CONCLUSIONS: AWS is a notable complication of ASLNB for melanoma, with an incidence as high or higher than "standard" complications. AWS should, therefore, be included in the preoperative discussion of possible complications of ASLNB. Traditional patient, tumor, and nodal factors are not predictive of AWS. Patients should be counseled that AWS usually responds to symptomatic treatment and resolves with time.

Sdrulla, A., & Chen, G. (2016). Minimally invasive procedures for neuropathic pain. *Pain Management*, 6(2), 103-109.

Neuropathic pain is "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system". The prevalence of neuropathic pain ranges from 7 to 11% of the population and minimally invasive procedures have been used to both diagnose and treat neuropathic pain. Diagnostic procedures consist of nerve blocks aimed to isolate the peripheral nerve implicated, whereas therapeutic interventions either modify or destroy nerve function. Procedures that modify how nerves function include epidural steroid injections, peripheral nerve blocks and sympathetic nerve blocks. Neuroablative procedures include radiofrequency ablation, cryoanalgesia and neurectomies. Currently, neuromodulation with peripheral nerve stimulators and spinal cord stimulators are the most evidence-based treatments of neuropathic pain.

Sharma, S. M., & Rosenbaum, J. T. (2016). Psoriasis. (pp. 713-718) Springer Berlin Heidelberg.

Psoriasis is a multisystem inflammatory disease which affects the skin with a prevalence of 1–2 % in the United States and Europe, but it is virtually absent in Africa and only 0.1 % in Asia. Males and females are affected equally by the skin disease, which has a mean age of onset of 30 years with the range being anytime from infancy to old age. © Springer-Verlag Berlin Heidelberg 2016.

Sharp, M. E., Caccappolo, E., Mejia-Santana, H., Tang, M. -, Rosado, L., Orbe Reilly, M., et al.

(2015). The relationship between obsessive-compulsive symptoms and PARKIN genotype: The CORE-PD study. *Movement Disorders*, 30(2), 278-283.

Background: Few studies have systematically investigated the association between PARKIN genotype and psychiatric co-morbidities of Parkinson's disease (PD). PARKIN-associated PD is characterized by severe nigral dopaminergic neuronal loss, a finding that may have implications for behaviors rooted in dopaminergic circuits such as obsessive-compulsive symptoms (OCS). Methods: The Schedule of Compulsions and Obsessions Patient Inventory (SCOPI) was administered to 104 patients with early-onset PD and 257 asymptomatic first-degree relatives. Carriers of one and two PARKIN mutations were compared with noncarriers. Results: Among patients, carriers scored lower than noncarriers in adjusted models (one-mutation: 13.9 point difference, $P=0.03$; two-mutation: 24.1, $P=0.001$), where lower scores indicate less OCS. Among asymptomatic relatives, a trend toward the opposite was seen: mutation carriers scored higher than noncarriers (one mutation, $P=0.05$; two mutations, $P=0.13$). Conclusions: First, a significant association was found between PARKIN mutation status and obsessive-compulsive symptom level in both PD and asymptomatic patients, suggesting that OCS might represent an early non-motor dopamine-dependent feature. Second, irrespective of disease status, heterozygotes were significantly different from noncarriers, suggesting that PARKIN heterozygosity may contribute to phenotype. © 2014 International Parkinson and Movement Disorder Society.

Shaw, A. T., Gandhi, L., Gadgeel, S., Riely, G. J., Cetnar, J., West, H., et al. (2016). Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: A single-group, multicentre, phase 2 trial. *The Lancet Oncology*, 17(2), 234-242.

Background: Alectinib—a highly selective, CNS-active, ALK inhibitor—showed promising clinical activity in crizotinib-naïve and crizotinib-resistant patients with ALK-rearranged (ALK-positive) non-small-cell lung cancer (NSCLC). We aimed to assess the safety and efficacy of alectinib in patients with ALK-positive NSCLC who progressed on previous crizotinib. Methods: We did a phase 2 study at 27 centres in the USA and Canada. We enrolled patients aged 18 years or older with stage IIIB-IV, ALK-positive NSCLC who had progressed after crizotinib. Patients were treated with oral alectinib 600 mg twice daily until progression, death, or withdrawal. The primary endpoint was the proportion of patients achieving an objective response by an independent review committee using Response Evaluation Criteria in Solid Tumors, version 1.1. Response endpoints were assessed in the response-evaluable population (ie, patients with measurable

disease at baseline who received at least one dose of study drug), and efficacy and safety analyses were done in the intention-to-treat population (all enrolled patients). This study is registered with ClinicalTrials.gov, number NCT01871805. The study is ongoing and patients are still receiving treatment. Findings: Between Sept 4, 2013, and Aug 4, 2014, 87 patients were enrolled into the study (intention-to-treat population). At the time of the primary analysis (median follow-up 4.8 months [IQR 3.3-7.1]), 33 of 69 patients with measurable disease at baseline had a confirmed partial response; thus, the proportion of patients achieving an objective response by the independent review committee was 48% (95% CI 36-60). Adverse events were predominantly grade 1 or 2, most commonly constipation (31 [36%]), fatigue (29 [33%]), myalgia (21 [24%]), and peripheral oedema (20 [23%]). The most common grade 3 and 4 adverse events were changes in laboratory values, including increased blood creatine phosphokinase (seven [8%]), increased alanine aminotransferase (five [6%]), and increased aspartate aminotransferase (four [5%]). Two patients died: one had a haemorrhage (judged related to study treatment), and one had disease progression and a history of stroke (judged unrelated to treatment). Interpretation: Alectinib showed clinical activity and was well tolerated in patients with ALK-positive NSCLC who had progressed on crizotinib. Therefore, alectinib could be a suitable treatment for patients with ALK-positive disease who have progressed on crizotinib. Funding: F Hoffmann-La Roche. © 2016 Elsevier Ltd.

Shaw, G. E., & Khalil, M. A. K. (1989). *Arctic haze* Springer Verlag.

Arctic haze is the pseudonym for large-scale industrial air pollution found all through the arctic air mass. It is perhaps in areal extent the most extensive air pollution system so far identified, affecting as it does approximately 9 percent of the earth's surface (an area larger than the African continent) when at its maximum size and strength in January to April. It is the result of strong meridional air currents that surge northward over central to western Eurasia carrying polluted air to the arctic basin. The arctic air mass is dark, cold, stable and stratified, all of which are characteristics that slow the removal of material from the atmosphere. Arctic haze has built up since the industrial revolution, but the pace has quickened since the Second World War as industry evolves northward. Pollution material in arctic haze is of a submicron size and contains a fraction of black carbon: it interacts strongly with solar radiation. In springtime, the atmosphere

is heated by an additional 5-20 W m^{-2} . The chemistry of arctic haze is fascinating since it represents an affected air mass in a sort of equilibrium state. Sulfate, mostly as H_2SO_4 , graphitic carbon, and a wide range of heavy metals in higher concentration than in strongly enriched crustal material are the predominant constituents of the particulate arctic air pollution. In addition, the polluted air reaching the arctic brings with it dozens of man-made gaseous pollutants; these can serve as indicators of the original arctic pollution. © 1989 Springer-Verlag Berlin Heidelberg.

Shen, J., Leslie, W. D., Nielson, C. M., Majumdar, S. R., Morin, S. N., & Orwoll, E. S. (2016).

Associations of body mass index with incident fractures and hip structural parameters in a large Canadian cohort. *Journal of Clinical Endocrinology and Metabolism*, 101(2), 476-484.

Context: Fractures in obese individuals are of public health importance, but the relationship between obesity and fracture is complex and remains poorly understood. Objective: The study examined the association of body mass index (BMI) with bone structural and strength parameters and incident fracture. Design and Setting: We performed cross-sectional and longitudinal analyses using data from the Manitoba Bone Density Program. Participants: We included 51 313 women and 4689 men aged 50 years or older referred for dual-energy X-ray absorptiometry scans. For 41 919 women and 4085 men, we were able to derive hip structural parameters. Main Outcome Measure: Cross-sectional moment of inertia, cross-sectional area, and femoral strength index were derived from dual-energy X-ray absorptiometry. Health service records were assessed for incident major osteoporotic fractures (MOFs) (mean follow-up 6.2 y in women and 4.7 y in men). Results: Among individuals with a BMI of less than 30 kg/m^2 , increasing BMI was associated with progressive increases in bone mineral density (BMD), cross-sectional moment of inertia, and cross-sectional area. The relationship reached a plateau around a BMI of 30 kg/m^2 , with little additional increment with further increases in BMI (all P for interaction $<.0001$, obese vs nonobese). Increasing BMI was linearly associated with decreases in strength index in both women and men. MOFs were ascertained in 3721 women and 276 men (1027 female and 75 male hip fractures). Higher BMI was associated with a lower risk of MOF in women in multivariable models, but this association was largely explained by their higher BMD. Protective association of higher BMI with hip fracture were stronger and only partially explained by BMD (hazard ratio

95% confidence interval] 0.79 0.73-0.99] for obese I and 0.67 0.46-0.98] for obese II). Higher BMI was not significantly associated with a risk of MOF or hip fracture in men. Conclusions: Despite structural and biomechanical disadvantages, obese women were at lower risk of fracture.

Sihag, S., Kosinski, A. S., Gaisert, H. A., Wright, C. D., & Schipper, P. H. (2016). Minimally invasive versus open esophagectomy for esophageal cancer: A comparison of early surgical outcomes from the society of thoracic surgeons national database. *Annals of Thoracic Surgery*, *101*(4), 1281-1288.

Background Open esophagectomy results in significant morbidity and mortality. Minimally invasive esophagectomy (MIE) has become increasingly popular at specialized centers with the aim of improving perioperative outcomes. Numerous single-institution studies suggest MIE may offer lower short-term morbidity. The two approaches are compared using a large, multiinstitutional database. **Methods** The Society of Thoracic Surgeons (STS) National Database (v2.081) was queried for all resections performed for esophageal cancer between 2008 and 2011 (n = 3,780). Minimally invasive approaches included both transhiatal (n = 214) and Ivor Lewis (n = 600), and these were compared directly with open transhiatal (n = 1,065) and Ivor Lewis (n = 1,291) procedures, respectively. Thirty-day outcomes were examined using nonparametric statistical testing. **Results** Both open and MIE groups were similar in terms of preoperative risk factors. Morbidity and all-cause mortality were equivalent at 62.2% and 3.8%. MIE was associated with longer median procedure times (443.0 versus 312.0 minutes; p < 0.001), but a shorter median length of hospital stay (9.0 versus 10.0 days; p < 0.001). Patients who underwent MIE had higher rates of reoperation (9.9% versus 4.4%; p < 0.001) and empyema (4.1% versus 1.8%; p < 0.001). Open technique led to an increased rate of wound infections (6.3% versus 2.3%; p < 0.001), postoperative transfusion (18.7% versus 14.1%; p = 0.002), and ileus (4.5% versus 2.2%; p = 0.002). Propensity score-matched analysis confirmed these findings. High- and low-volume centers had similar outcomes. **Conclusions** Early results from the STS National Database indicate that MIE is safe, with comparable rates of morbidity and mortality as open technique. Longer procedure times and a higher rate of reoperation following MIE may reflect a learning curve. © 2016 The Society of Thoracic Surgeons.

Sileikyte, J., & Forte, M. (2016). Shutting down the pore: The search for small molecule inhibitors of the mitochondrial permeability transition. *Biochimica Et Biophysica Acta*,
The mitochondrial permeability transition pore (PTP) is now recognized as playing a key role in a wide variety of human diseases whose common pathology may be based in mitochondrial dysfunction. Recently, PTP assays have been adapted to high-throughput screening approaches to identify small molecules specifically inhibiting the PTP. Following extensive secondary chemistry, the most potent inhibitors of the PTP described to date have been developed. This review will provide an overview of each of these screening efforts, use of resulting compounds in animal models of PTP-based diseases, and problems that will require further study.

Simpson, E. L., Bieber, T., Eckert, L., Wu, R., Ardeleanu, M., Graham, N. M. H., et al. (2016). Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *Journal of the American Academy of Dermatology*, 74(3), 491-498.
Background The adult burden of atopic dermatitis (AD) is poorly characterized. Objective We sought to characterize AD burden in adults with moderate to severe disease from the patient's perspective. Methods Patient-reported outcomes collected at screening in a phase 2b clinical trial of dupilumab included pruritus numeric rating scale, 5-Dimension Pruritus Scale, subjective components of SCORing AD, Patient-Oriented Eczema Measure, Hospital Anxiety and Depression Scale, Dermatology Life Quality Index, and 5-Dimension EuroQol. Results Most of the 380 patients had been living with AD for nearly all their lives, whereas approximately 40% were given a diagnosis as adults; 40.3% had asthma and 60.5% had other allergic conditions. Despite 48.2% of patients using systemic therapies in the past year, patients reported problems with itch frequency (85% of patients), duration (41.5% reported itching ≥ 18 h/d), and severity (6.5 of 10 on numeric rating scale); 55% reported AD-related sleep disturbances 5 d/wk or more. Hospital Anxiety and Depression Scale scores suggesting clinically relevant anxiety or depression were reported by 21.8% of patients. Quality of life was impaired on Dermatology Life Quality Index and 5-dimension EuroQol. Limitations This study had limited generalizability; conclusions may not reflect those with mild AD or not participating in a clinical trial. Conclusions Adults with moderate to severe AD report multidimensional burden including disease activity, patient-reported

symptoms, comorbidities, and quality-of-life impact. © 2015 American Academy of Dermatology, Inc.

Smith, B. A., Carlson-Kuhta, P., & Horak, F. B. (2016). Consistency in administration and response for the backward push and release test: A clinical assessment of postural responses. *Physiotherapy Research International*, 21(1), 36-46.

Background and Purpose: The backward push and release test (PRT) is a standardized clinical test of postural responses elicited by perturbations. Our goal was to determine reliability of administration and response. This will inform clinical administration and determine whether to develop an instrumented version. **Methods:** One examiner administered 10 backward PRT trials to adults with Parkinson disease (12), multiple sclerosis (14) and controls (12). We used three-dimensional motion analysis, force plates and instrumented gloves to measure administration and response. Administration variables were angle of posterior trunk lean and the distance of the centre of mass (CoM) behind the ankle. Postural response variables were latency of postural response from release to step initiation and first compensatory step length. Reliability was measured using the range of variables across trials, comparison of first and later trials, intraclass correlations (ICCs) to measure consistency and correlations between administration and response. **Results:** There was inherent variability in administration, which affected postural response characteristics. Larger trunk angle and greater CoM-ankle distance were correlated with shorter postural response latencies and larger step lengths. Participant height also had an effect; taller participants had larger trunk angles prior to release resulting in longer latencies and larger step lengths. Using ICCs, consistency of trunk angle was likely acceptable and CoM-ankle distance was high. Consistency of latency was low, while step length was likely acceptable. **Discussion:** Despite variability in administration and inconsistency in response, different postural response characteristics were detected between patients with different disease states. Based on these results, we will create algorithms to instrument the PRT using inertial movement sensors to collect more sensitive measures of postural responses than observational clinical rating scales. Feedback for appropriate lean angle and calibration for participant height will improve consistency and usefulness of the instrumented PRT. © 2016 John Wiley & Sons, Ltd.

Smith, J. R., Stempel, A. J., Bharadwaj, A., & Appukuttan, B. (2016). Involvement of B cells in non-infectious uveitis. *Clinical & Translational Immunology*, 5(2), e63.

Non-infectious uveitis-or intraocular inflammatory disease-causes substantial visual morbidity and reduced quality of life amongst affected individuals. To date, research of pathogenic mechanisms has largely been focused on processes involving T lymphocyte and/or myeloid leukocyte populations. Involvement of B lymphocytes has received relatively little attention. In contrast, B-cell pathobiology is a major field within general immunological research, and large clinical trials have showed that treatments targeting B cells are highly effective for multiple systemic inflammatory diseases. B cells, including the terminally differentiated plasma cell that produces antibody, are found in the human eye in different forms of non-infectious uveitis; in some cases, these cells outnumber other leukocyte subsets. Recent case reports and small case series suggest that B-cell blockade may be therapeutic for patients with non-infectious uveitis. As well as secretion of antibody, B cells may promote intraocular inflammation by presentation of antigen to T cells, production of multiple inflammatory cytokines and support of T-cell survival. B cells may also perform various immunomodulatory activities within the eye. This translational review summarizes the evidence for B-cell involvement in non-infectious uveitis, and considers the potential contributions of B cells to the development and control of the disease. Manipulations of B cells and/or their products are promising new approaches to the treatment of non-infectious uveitis.

Smith, J. S., Klineberg, E., Lafage, V., Shaffrey, C. I., Schwab, F., Lafage, R., et al. (2016).

Prospective multicenter assessment of perioperative and minimum 2-year postoperative complication rates associated with adult spinal deformity surgery. *Journal of Neurosurgery.Spine*, 1-14.

OBJECTIVE Although multiple reports have documented significant benefit from surgical treatment of adult spinal deformity (ASD), these procedures can have high complication rates. Previously reported complications rates associated with ASD surgery are limited by retrospective design, single-surgeon or single-center cohorts, lack of rigorous data on complications, and/or limited follow-up. Accurate definition of complications associated with ASD surgery is important and may serve as a resource for patient counseling and efforts to improve the safety of patient

care. The authors conducted a study to prospectively assess the rates of complications associated with ASD surgery with a minimum 2-year follow-up based on a multicenter study design that incorporated standardized data-collection forms, on-site study coordinators, and regular auditing of data to help ensure complete and accurate reporting of complications. In addition, they report age stratification of complication rates and provide a general assessment of factors that may be associated with the occurrence of complications. METHODS As part of a prospective, multicenter ASD database, standardized forms were used to collect data on surgery-related complications. On-site coordinators and central auditing helped ensure complete capture of complication data. Inclusion criteria were age older than 18 years, ASD, and plan for operative treatment. Complications were classified as perioperative (within 6 weeks of surgery) or delayed (between 6 weeks after surgery and time of last follow-up), and as minor or major. The primary focus for analyses was on patients who reached a minimum follow-up of 2 years. RESULTS Of 346 patients who met the inclusion criteria, 291 (84%) had a minimum 2-year follow-up (mean 2.1 years); their mean age was 56.2 years. The vast majority (99%) had treatment including a posterior procedure, 25% had an anterior procedure, and 19% had a 3-column osteotomy. At least 1 revision was required in 82 patients (28.2%). A total of 270 perioperative complications (145 minor; 125 major) were reported, with 152 patients (52.2%) affected, and a total of 199 delayed complications (62 minor; 137 major) were reported, with 124 patients (42.6%) affected. Overall, 469 complications (207 minor; 262 major) were documented, with 203 patients (69.8%) affected. The most common complication categories included implant related, radiographic, neurological, operative, cardiopulmonary, and infection. Higher complication rates were associated with older age ($p = 0.009$), greater body mass index ($p \leq 0.031$), increased comorbidities ($p \leq 0.007$), previous spine fusion ($p = 0.029$), and 3-column osteotomies ($p = 0.036$). Cases in which 2-year follow-up was not achieved included 2 perioperative mortalities (pulmonary embolus and inferior vena cava injury). CONCLUSIONS This study provides an assessment of complications associated with ASD surgery based on a prospective, multicenter design and with a minimum 2-year follow-up. Although the overall complication rates were high, in interpreting these findings, it is important to recognize that not all complications are equally impactful. This study represents one of the most complete and detailed reports of perioperative and delayed complications associated with ASD surgery to date. These findings may prove useful

for treatment planning, patient counseling, benchmarking of complication rates, and efforts to improve the safety and cost-effectiveness of patient care.

Smith, K., Neville-Jan, A., Freeman, K. A., Adams, E., Mizokawa, S., Dudgeon, B. J., et al. (2016). The effectiveness of bowel and bladder interventions in children with spina bifida. *Developmental Medicine and Child Neurology*,

AIM: Using the World Health Organization International Classification of Functioning, Disability and Health (ICF), the aim of this study was to identify effective strategies for managing urinary and bowel complications resulting from spina bifida. METHOD: Charts of 210 children between 4- and 13-years-old with spina bifida were reviewed to quantify medical interventions and continence status. Standardized quality of life (QOL) questionnaires were administered to a subset of participants; child and parent interviews were carried out to examine the experience of living with bowel and bladder incontinence. Practitioners were also interviewed to understand their perspectives of intervention effectiveness. RESULTS: Chart review indicated less than half of children were continent for bowel and bladder. More variability existed in bowel continence programs, and practitioners considered bowel continence more difficult to achieve than bladder continence. No significant associations were found between continence status and QOL measures. Interviews, however, reflected how managing continence at home and school more broadly affects QOL. Among practitioners, some focused primarily on optimizing physical health while others focused on activity and participation. INTERPRETATION: While continence is a goal, programs used to achieve this are individualized and outcomes may be affected by differential treatment effects, environmental factors, and/or stigma experienced by children.

Solopova, I. A., Selionov, V. A., Zhvansky, D. S., Gurfinkel, V. S., & Ivanenko, Y. (2016). Human cervical spinal cord circuitry activated by tonic input can generate rhythmic arm movements. *Journal of Neurophysiology*, *115*(2), 1018-1030.

The coordination between arms and legs during human locomotion shares many features with that in quadrupeds, yet there is limited evidence for the central pattern generator for the upper limbs in humans. Here we investigated whether different types of tonic stimulation, previously used for eliciting stepping-like leg movements, may evoke nonvoluntary rhythmic arm

movements. Twenty healthy subjects participated in this study. The subject was lying on the side, the trunk was fixed, and all four limbs were suspended in a gravity neutral position, allowing unrestricted low-friction limb movements in the horizontal plane. The results showed that peripheral sensory stimulation (continuous muscle vibration) and central tonic activation (postcontraction state of neuronal networks following a long-lasting isometric voluntary effort, Kohnstamm phenomenon) could evoke nonvoluntary rhythmic arm movements in most subjects. In ~40% of subjects, tonic stimulation elicited nonvoluntary rhythmic arm movements together with rhythmic movements of suspended legs. The fact that not all participants exhibited nonvoluntary limb oscillations may reflect interindividual differences in responsiveness of spinal pattern generation circuitry to its activation. The occurrence and the characteristics of induced movements highlight the rhythmogenesis capacity of cervical neuronal circuitries, complementing the growing body of work on the quadrupedal nature of human gait. © 2016 the American Physiological Society.

Sourati, J., Erdogmus, D., Akcakaya, M., Kazmierczak, S. C., & Leen, T. K. (2015). A novel delta check method for detecting laboratory errors. , *2015-November*.

Investigating the variation of clinical measurements of patients over time is a common technique, known as delta check, for detecting laboratory errors. They are based on the expected biological variations and machine imprecision, where the latter varies for different concentrations of the analytes. Here, we present a novel delta check method in the form of composite thresholding, and provide its sufficient statistics by constructing the corresponding discriminant function, which enables us to use statistical and learning analysis tools. Using the scores obtained from such a discriminant function, we statistically study the performance of our algorithm on a labeled data set for the purpose of detecting lab errors. © 2015 IEEE.

Sparks, T. N., Griffin, E., Page, J., Pilliod, R., Shaffer, B. L., & Caughey, A. B. (2016). Down syndrome: Perinatal mortality risks with each additional week of expectant management. *Prenatal Diagnosis*,

Objective: To evaluate the gestational age (GA) at which perinatal mortality risk is minimized for fetuses with Down syndrome (DS). Methods: Retrospective cohort of singleton pregnancies

delivered between 24 and 41 weeks, using 2005-2006 United States linked birth and death certificate data. Among fetal DS cases, prospective risk of intrauterine fetal demise (IUFD) and risk of infant death were calculated for each week, and composite risk of fetal/infant mortality with expectant management was compared to delivery. Results: Of 3113098 pregnancies, 1766 had fetal DS (0.06%). IUFD occurred in 7.4% with DS, and infant death in 6.5%. Prospective risk of IUFD increased from 37 weeks onward to reach 50.7 per 1000 pregnancies (95% CI 33.2-68.3) at 42 weeks. Comparing mortality with expectant management to delivery, expectant management carried increasing risk from 38 (RR 1.18; 95% CI 1.05-1.33) to 41 weeks (RR 1.84; 95% CI 1.66-2.05). Further, number needed to deliver to avoid one excess death decreased from 38 (109.17; 95% CI 64.52-344.83) to 41 weeks (24.08; 95% CI 20.59-29.04). Conclusions: Although further research is needed to clarify risk factors for fetal and neonatal death in cases of DS, risk of perinatal mortality appears to be minimized with delivery at 38 weeks. © 2016 John Wiley & Sons, Ltd.

Stevens, B., Maxson, J., Tyner, J., Smith, C. A., Gutman, J. A., Robinson, W., et al. (2016). Clonality of neutrophilia associated with plasma cell neoplasms: Report of a SETBP1 mutation and analysis of a single institution series. *Leukemia and Lymphoma*, 57(4), 927-934.

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 3-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. © 2015 Taylor & Francis.

Stewart, I. J., Faulk, T. I., Sosnov, J. A., Clemens, M. S., Elterman, J., Ross, J. D., et al. (2016).

Rhabdomyolysis among critically ill combat casualties: Associations with acute kidney injury and mortality. *Journal of Trauma and Acute Care Surgery*, 80(3), 492-498.

BACKGROUND: Rhabdomyolysis has been associated with poor outcomes in patients with traumatic injury, especially in the setting of acute kidney injury (AKI). However, rhabdomyolysis has not been systematically examined in a large cohort of combat casualties injured in the wars in Iraq and Afghanistan. METHODS: We conducted a retrospective study of casualties injured during combat operations in Iraq and Afghanistan who were initially admitted to the intensive care unit from February 1, 2002, to February 1, 2011. Information on age, sex, Abbreviated Injury Scale (AIS) score, Injury Severity Score (ISS), mechanism of injury, shock index, creatine kinase, and serum creatinine were collected. These variables were examined via multivariate logistic and Cox regression analyses to determine factors independently associated with rhabdomyolysis, AKI, and death. RESULTS: Of 6,011 admissions identified, a total of 2,109 patients met inclusion criteria and were included for analysis. Rhabdomyolysis, defined as creatine kinase greater than 5,000 U/L, was present in 656 subjects (31.1%). Risk factors for rhabdomyolysis identified on multivariable analysis included injuries to the abdomen and extremities, increased ISS, male sex, explosive mechanism of injury, and shock index greater than 0.9. After adjustment, patients with rhabdomyolysis had a greater than twofold increase in the odds of AKI. In the analysis for mortality, rhabdomyolysis was significantly associated with death until AKI was added, at which point it lost statistical significance. CONCLUSION: We found that rhabdomyolysis is associated with the development of AKI in combat casualties. While rhabdomyolysis was strongly associated with mortality on the univariate model and in conjunction with both ISS and age, it was not associated with mortality after the inclusion of AKI. This suggests that the effect of rhabdomyolysis on mortality may be mediated by AKI. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

Strehl, C., Bijlsma, J. W., de Wit, M., Boers, M., Caeyers, N., Cutolo, M., et al. (2016). Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: Viewpoints from an EULAR task force. *Annals of the Rheumatic Diseases*,

There is convincing evidence for the known and unambiguously accepted beneficial effects of glucocorticoids at low dosages. However, the implementation of existing recommendations and guidelines on the management of glucocorticoid therapy in rheumatic diseases is lagging behind. As a first step to improve implementation, we aimed at defining conditions under which long-term glucocorticoid therapy may have an acceptably low level of harm. A multidisciplinary European League Against Rheumatism task force group of experts including patients with rheumatic diseases was assembled. After a systematic literature search, breakout groups critically reviewed the evidence on the four most worrisome adverse effects of glucocorticoid therapy (osteoporosis, hyperglycaemia/diabetes mellitus, cardiovascular diseases and infections) and presented their results to the other group members following a structured questionnaire for final discussion and consensus finding. Robust evidence on the risk of harm of long-term glucocorticoid therapy was often lacking since relevant study results were often either missing, contradictory or carried a high risk of bias. The group agreed that the risk of harm is low for the majority of patients at long-term dosages of 10 mg/day the risk of harm is elevated. At dosages between >5 and ≤ 10 mg/day, patient-specific characteristics (protective and risk factors) determine the risk of harm. The level of harm of glucocorticoids depends on both dose and patient-specific parameters. General and glucocorticoid-associated risk factors and protective factors such as a healthy lifestyle should be taken into account when evaluating the actual and future risk.

Stubbs, G., Henley, K., & Green, J. (2016). Autism: Will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings? *Medical Hypotheses*, 88, 74-78.

Background: Vitamin D deficiency is widespread in the world including the vulnerable group of pregnant women. Vitamin D deficiency during pregnancy is hypothesized to contribute to the cause of autism. Further, it is hypothesized that vitamin D supplementation during pregnancy and early childhood will reduce the recurrence rate of autism in newborn siblings. Methods: To investigate the hypothesis an open label prospective study was performed prescribing vitamin D during pregnancy to mothers of children with autism at a dose of 5000 IU/day. The newborn siblings were at high risk for the recurrence of autism. The newborn infants were also prescribed vitamin D, 1000 IU/day to their third birthday. The newborn siblings were followed for three

years and during that time, were assessed for autism on two separate occasions: at 18 months and 36 months of age. The results were compared to the reported recurrence rates in siblings of autistic children in the literature. Results: The final outcome was 1 out of 19 (5%) developed autism in contrast to the recurrence rate of approximately 20% in the literature. We did not have a control group, nor was there blinding. Conclusions: The results are promising, however, this is a preliminary study with very small numbers and was uncontrolled. Further study with larger numbers is indicated. The ethics of prescribing a low dosage of vitamin D such as 400 IU D3/day to a control group of mothers in comparison to a large dose such as 5000 IU D3/day are problematic in our opinion. © 2016 The Authors.

Stumbo, S. P., Yarborough, B. J. H., Janoff, S. L., Yarborough, M. T., McCarty, D., & Green, C. A. (2016). A qualitative analysis of family involvement in prescribed opioid medication monitoring among individuals who have experienced opioid overdoses. *Substance Abuse*, , 1-8.

Background: Little is known about the role, extent, or effects of family member involvement in monitoring and managing opioid analgesics. Knowing when or how family members monitor prescribed opioid medication taking, whether it is acceptable to patients, or how family relationships may be affected by monitoring, are not well documented. Methods: The study was conducted at Kaiser Permanente Northwest, an integrated health plan in Oregon and Washington. Semistructured in-depth interviews (N = 87) assessed circumstances surrounding overdose events among individuals who either experienced an opioid-related overdose or were family members of patients who died as a result of such an overdose. A subset of participants (n = 20) described family members' roles in monitoring opioid medications before or after overdoses. Interviews were transcribed verbatim and coded using Atlas.ti. We used a modified grounded theory approach to categorize emergent data and to identify common themes. Results: When family members played roles in monitoring and managing opioid medications, clinicians were often unaware of their involvement. Patients and family members reported better outcomes when the patient, caregiver, and clinician developed a shared treatment plan. Negative outcomes included relationship stress, particularly when patients and caregivers had differing perspectives about what constituted effective pain management versus misuse and abuse. Conclusions: When families are concerned about opioid medications, coordination between clinicians, patients, and

family carers appears to clarify roles and foster better outcomes. Increased stress and worse outcomes were reported when clinicians were not actively involved and when they did not attend to carers' concerns. © 2016 Taylor & Francis Group, LLC

Suhler, E. B., & Biggee, K. (2016). Methotrexate. (pp. 355-361) Springer Berlin Heidelberg.

Methotrexate is a member of the antimetabolite drug class. Drugs in this classification, including methotrexate, azathioprine, mycophenolate mofetil, and leflunomide, exert anti-inflammatory activity via their effect on DNA synthesis, which suppresses proliferation of rapidly dividing cells, including leukocytes, as well as by other mechanisms which are incompletely understood.

Methotrexate has the longest track record for safety and efficacy of all the antimetabolites both in children and in adults, and this, combined with its relatively low cost and the convenience of once-weekly administration, makes it the first-line steroid-sparing immunosuppressive for many ocular and systemic inflammatory diseases. Its use was first described in the 1940s for treatment of malignant diseases, but it was found shortly thereafter to be useful for inflammatory diseases, including rheumatoid arthritis, for which it gained FDA approval in 1988. Although methotrexate, like all other commercially available immunosuppressives as of this writing, is not FDA approved for the treatment of uveitis, it is FDA approved for two diseases associated with uveitis, psoriatic arthritis and juvenile idiopathic arthritis. The off-label use of methotrexate for uveitis was first reported in 1965 and has been commonly reported since, both as monotherapy and in combination with other immunosuppressives. A recent survey of practice patterns among uveitis specialists cited methotrexate as the most commonly prescribed initial corticosteroid-sparing agent for all anatomic locations of uveitis and the most preferred agent for anterior uveitis. © Springer-Verlag Berlin Heidelberg 2016.

Sun, B. C., Laurie, A., Fu, R., Ferencik, M., Shapiro, M., Lindsell, C. J., et al. (2016). Comparison of the HEART and TIMI risk scores for suspected acute coronary syndrome in the emergency department. *Critical Pathways in Cardiology*, 15(1), 1-5.

Objectives: The emergency department evaluation for suspected acute coronary syndrome (ACS) is common, costly, and challenging. Risk scores may help standardize clinical care and screening for research studies. The Thrombolysis in Myocardial Infarction (TIMI) and HEART are

two commonly cited risk scores. We tested the null hypothesis that the TIMI and HEART risk scores have equivalent test characteristics. Methods: We analyzed data from the Internet Tracking Registry of Acute Coronary Syndromes (iâ—TrAC S) from 9 EDs on patients with suspected AC S, 1999-2001. We excluded patients with an emergency department diagnosis consistent with AC S, or without sufficient data to calculate TIMI and HEART scores. The primary outcome was 30-day major adverse cardiovascular events, including all-cause death, acute myocardial infarction, and urgent revascularization. We describe test characteristics of the TIMI and HEART risk scores. Results: The study cohort included 8255 patients with 508 (6.2%) 30-day major adverse cardiovascular events. Receiver operating curve and reclassification analyses favored HEART c statistic: 0.753, 95% confidence interval (CI): 0.733-0.773; continuous net reclassification improvement: 0.608, 95% CI: 0.527-0.689] over TIMI (c statistic: 0.678, 95% CI: 0.655-0.702). A HEART score 0-3 negative predictive value (NPV) 0.982, 95% CI: 0.978-0.986; positive predictive value (PPV) 0.103, 95% CI: 0.094-0.113; likelihood ratio (LR) positive 1.76; LR negative 0.28] demonstrates similar or superior NPV/PPV/LR compared with TIMI = 0 (NPV 0.978, 95% CI: 0.971-0.983; PPV 0.077, 95% CI: 0.071-0.084; LR positive 1.28; LR negative 0.35) and TIMI = 0-1 (NPV 0.963, 95% CI: 0.958-0.968; PPV 0.102, 95% CI: 0.092-0.113; LR positive 1.73; LR negative 0.58). Conclusions: The HEART score has better discrimination than TIMI and outperforms TIMI within previously published "low-risk" categories. Â© 2016 Wolters Kluwer Health, Inc. All rights reserved.

Sundfeld, D., Correr-Sobrinho, L., Pini, N. I., Costa, A. R., Sundfeld, R. H., Pfeifer, C. S., et al. (2016).

Heat treatment-improved bond strength of resin cement to lithium disilicate dental glass-ceramic. *Ceramics International*,

This study investigated the influence of different hydrofluoric acid (HF) concentrations and heat treatments applied to a lithium disilicate dental glass-ceramic (EMX) on surface morphology and micro-shear bond strength (Î¼SBS) to resin cement. Five HF concentrations (1%, 2.5%, 5%, 7.5% and 10%) and four different heat treatments applied before etching were assessed: 1. etching at room temperature with no previous heat treatment (control group); 2. HF stored at 70. Â°C for 1. min applied to the ceramic surface at room temperature; 3. HF at room temperature applied after a hot air stream is applied perpendicularly to the ceramic surface for 1.

min; 4. the combination of previously heated HF and heated EMX surface. The etching time was fixed for 20. s for all groups. Etched EMX specimens were analyzed on field-emission scanning electron microscope (FE-SEM) and the $\hat{I}^{\frac{1}{4}}$ SBS was carried out on a universal testing machine at a crosshead speed of 1 mm/min until fracture. For the control groups, FE-SEM images showed greater glassy matrix dissolution and higher $\hat{I}^{\frac{1}{4}}$ SBS for 7.5% and 10% HF concentrations. The previous heat treatments enhanced the glassy matrix dissolution more evidently for 1%, 2.5% and 5% and yielded increased $\hat{I}^{\frac{1}{4}}$ SBS values, which were not statistically different for 7.5% and 10% HF concentrations (control group). HF concentrations and previous heat treatments did show to have an influence on the etching/bonding characteristics to lithium disilicate dental glass-ceramic. © 2016 Elsevier Ltd and Techna Group S.r.l.

Sunstrom, R., Hamilton, N., Fialkowski, E., Lofberg, K., McKee, J., Sims, T., et al. (2016). Minimizing variance in pediatric gastrostomy: Does standardized perioperative feeding plan decrease cost and improve outcomes? *American Journal of Surgery*,

BACKGROUND: A protocol for laparoscopic gastrostomy placement was implemented which specified perioperative antibiotics, feeding regimens, and discharge criteria. Our hypothesis was that hospital cost could be decreased, whereas at the same time improving or maintaining patient outcomes. METHODS: Data were collected on consecutive patients beginning 6 months after implementation of our protocol. We recorded surgeon compliance, patient outcomes (as defined by 30-day NSQIP complication rates), and cost of initial hospitalization, which was then compare to a 6-month historical control period. RESULTS: Our control group n = 26 and protocol group n = 39. Length of stay was shorter in the protocol group (P \leq .05 by nonparametric analysis). The complication rate was similar in both groups (23% control vs 15% protocol, P = .43). Initial hospital costs were not different. Surgeon compliance to protocol was 82%. CONCLUSIONS: A standard protocol is achievable for gastrostomy tube management. After implementation of our protocol, we were able to show a significant decrease in length of stay, whereas maintaining quality.

Sylwester, A., Nambiar, K. Z., Caserta, S., Klenerman, P., Picker, L. J., & Kern, F. (2016). A new perspective of the structural complexity of HCMV-specific T-cell responses. *Mechanisms of Ageing*

and Development,

BACKGROUND: In studies exploring the effects of HCMV infection on immune system aging ('immunosenescence'), after organ transplantation or in other settings, HCMV-specific T-cell responses are often assessed with respect to purportedly 'immunodominant' protein subunits. However, the response structure in terms of recognized antigens and response hierarchies (architecture) is not well understood and actual correlates of immune protection are not known.

METHODS: We explored the distribution of T-cell response sizes and dominance hierarchies as well as response breadth in 33 HCMV responders with respect to >200 HCMV proteins. **RESULTS:** At the individual responder level HCMV-specific T-cell responses were generally arranged in clear dominance hierarchies; interestingly, the number of proteins recognized by an individual correlated closely with the size of their biggest response. Target-specificity varied considerably between donors and across hierarchy levels with the presence, size, and hierarchy position of responses to purportedly 'immunodominant' targets being unpredictable. **CONCLUSIONS:** Predicting protective immunity based on isolated HCMV subunit-specific T-cell responses is questionable in light of the complex architecture of the overall response. Our findings have important implications for T-cell monitoring, intervention strategies, as well as the application of animal models to the understanding of human infection.

Terauchi, Y., Koyama, M., Cheng, X., Takahashi, Y., Riddle, M. C., Bolli, G. B., et al. (2016). New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: Glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). *Diabetes, Obesity and Metabolism*, 18(4), 366-374. **Aims:** To compare the efficacy and safety of insulin glargine 300 U/ml (Gla-300) with glargine 100 U/ml (Gla-100) in Japanese people with type 2 diabetes using basal insulin plus oral antihyperglycaemic drug(s) OAD(s)]. **Methods:** The EDITION JP 2 study (NCT01689142) was a 6-month, multicentre, open-label, phase III study. Participants (n = 241, male 61%, mean diabetes duration 14 years, mean weight 67 kg, mean body mass index 25 kg/m², mean glycated haemoglobin (HbA1c) 8.02 %, mean basal insulin dose 0.24 U/kg/day) were randomized to Gla-300 or Gla-100, while continuing OAD(s). Basal insulin was titrated to target fasting self-monitored plasma glucose 4.4-5.6 mmol/l. The primary efficacy endpoint was HbA1c change over

6 months. Safety endpoints included hypoglycaemia and weight change. Results: Gla-300 was non-inferior to Gla-100 for HbA1c reduction least squares (LS) mean difference 0.10 (95% confidence interval CI] -0.08, 0.27) %]. The mean HbA1c at month 6 was 7.56 and 7.52 % with Gla-300 and Gla-100, respectively. Nocturnal confirmed ($\hat{\alpha}\% \times 3.9$ mmol/l) or severe hypoglycaemia risk was 38% lower with Gla-300 versus Gla-100 relative risk 0.62 (95% CI 0.44, 0.88)]; annualized rates were 55% lower at night rate ratio 0.45 (95% CI 0.21, 0.96)] and 36% lower at any time 24 h; rate ratio 0.64 (95% CI 0.43, 0.96)]. Severe hypoglycaemia was infrequent. A significant between-treatment difference in weight change favoured Gla-300 LS mean difference -1.0 (95% CI -1.5, -0.5) kg; $p = 0.0003$]. Adverse event rates were comparable between groups. Conclusions: Japanese people with type 2 diabetes using basal insulin plus OAD(s) experienced less hypoglycaemia with Gla-300 than with Gla-100, while glycaemic control did not differ. © 2016 John Wiley & Sons Ltd.

Tereshchenko, L. G., Ghafoori, E., Kabir, M. M., & Kowalsky, M. (2015). Electrical dyssynchrony on noninvasive electrocardiographic mapping correlates with SAI QRST on surface ECG. *Computing in Cardiology*, 42, 69-72.

AIM: The goal of this study was to compare associations between clinical and ECG predictors of cardiac resynchronization therapy (CRT) response with electrical dyssynchrony. METHODS: Body-surface potentials were recorded using a 120-lead system in 4 patients (age 62 +/- 12 y, left ventricular ejection fraction (LVEF) 29 +/- 5 %; QRS duration 154 +/- 19 ms) with post-myocardial infarction scar and left bundle branch block before CRT implantation. A patient-specific heart-torso model derived from MRI with 291 heart-surface nodes was developed. Electrical dyssynchrony index (EDI) was computed as the standard deviation of activation times on the epicardium while uncoupling index (UI) was measured as the difference between the activation times. RESULTS: QRS duration correlated with mean activation time ($r = 0.977$; $P = 0.023$), but did not correlate with EDI or UI. LVEF inversely correlated with activation time at the lowest 20th percentile ($r = -0.960$; $P = 0.040$). Sum absolute QRST integral (SAI QRST), measured on orthogonal XYZ ECG, correlated with EDI ($r = 0.955$; $P = 0.045$), and characterized late-activated area of the left ventricle. CONCLUSION: SAI QRST is a measure of electrical dyssynchrony on ECG.

Than, K. D., Curran, J. N., Resnick, D. K., Shaffrey, C. I., Ghogawala, Z., & Mummaneni, P. V. (2016).

How to predict return to work after lumbar discectomy: Answers from the NeuroPoint-SD registry. *Journal of Neurosurgery.Spine*, , 1-6.

OBJECTIVE To date, the factors that predict whether a patient returns to work after lumbar discectomy are poorly understood. Information on postoperative work status is important in analyzing the cost-effectiveness of the procedure. **METHODS** An observational prospective cohort study was completed at 13 academic and community sites (NeuroPoint-Spinal Disorders [NeuroPoint-SD] registry). Patients undergoing single-level lumbar discectomy were included. Variables assessed included age, sex, body mass index (BMI), SF-36 physical function score, Oswestry Disability Index (ODI) score, presence of diabetes, smoking status, systemic illness, workers' compensation status, and preoperative work status. The primary outcome was working status within 3 months after surgery. Stepwise logistic regression analysis was performed to determine which factors were predictive of return to work at 3 months following discectomy. **RESULTS** There were 127 patients (of 148 total) with data collected 3 months postoperatively. The patients' average age at the time of surgery was 46 +/- 1 years, and 66.9% of patients were working 3 months postoperatively. Statistical analyses demonstrated that the patients more likely to return to work were those of younger age (44.5 years vs 50.5 years, $p = 0.008$), males (55.3% vs 28.6%, $p = 0.005$), those with higher preoperative SF-36 physical function scores (44.0 vs 30.3, $p = 0.002$), those with lower preoperative ODI scores (43.8 vs 52.6, $p = 0.01$), nonsmokers (83.5% vs 66.7%, $p = 0.03$), and those who were working preoperatively (91.8% vs 26.2%, $p < 0.0001$). When controlling for patients who were working preoperatively (105 patients), only age was a statistically significant predictor of postoperative return to work (44.1 years vs 51.1 years, $p = 0.049$). **CONCLUSIONS** In this cohort of lumbar discectomy patients, preoperative working status was the strongest predictor of postoperative working status 3 months after surgery. Younger age was also a predictor. Factors not influencing return to work in the logistic regression analysis included sex, BMI, SF-36 physical function score, ODI score, presence of diabetes, smoking status, and systemic illness. Clinical trial registration no.: 01220921 (clinicaltrials.gov).

Than, K. D., Park, P., Fu, K. M., Nguyen, S., Wang, M. Y., Chou, D., et al. (2016). Clinical and radiographic parameters associated with best versus worst clinical outcomes in minimally invasive spinal deformity surgery. *Journal of Neurosurgery.Spine*, , 1-5.

OBJECTIVE Minimally invasive surgery (MIS) techniques are increasingly used to treat adult spinal deformity. However, standard minimally invasive spinal deformity techniques have a more limited ability to restore sagittal balance and match the pelvic incidence-lumbar lordosis (PI-LL) than traditional open surgery. This study sought to compare "best" versus "worst" outcomes of MIS to identify variables that may predispose patients to postoperative success. **METHODS** A retrospective review of minimally invasive spinal deformity surgery cases was performed to identify parameters in the 20% of patients who had the greatest improvement in Oswestry Disability Index (ODI) scores versus those in the 20% of patients who had the least improvement in ODI scores at 2 years' follow-up. **RESULTS** One hundred four patients met the inclusion criteria, and the top 20% of patients in terms of ODI improvement at 2 years (best group, 22 patients) were compared with the bottom 20% (worst group, 21 patients). There were no statistically significant differences in age, body mass index, pre- and postoperative Cobb angles, pelvic tilt, pelvic incidence, levels fused, operating room time, and blood loss between the best and worst groups. However, the mean preoperative ODI score was significantly higher (worse disability) at baseline in the group that had the greatest improvement in ODI score (58.2 vs 39.7, $p < 0.001$). There was no difference in preoperative PI-LL mismatch (12.8 degrees best vs 19.5 degrees worst, $p = 0.298$). The best group had significantly less postoperative sagittal vertical axis (SVA; 3.4 vs 6.9 cm, $p = 0.043$) and postoperative PI-LL mismatch (10.4 degrees vs 19.4 degrees, $p = 0.027$) than the worst group. The best group also had better postoperative visual analog scale back and leg pain scores ($p = 0.001$ and $p = 0.046$, respectively). **CONCLUSIONS** The authors recommend that spinal deformity surgeons using MIS techniques focus on correcting a patient's PI-LL mismatch to within 10 degrees and restoring SVA to < 5 cm. Restoration of these parameters seems to impact which patients will attain the greatest degree of improvement in ODI outcomes, while the spines of patients who do the worst are not appropriately corrected and may be fused into a fixed sagittal plane deformity.

Thiele, D. K., & Anderson, C. M. (2016). Developmental origins of health and disease: A challenge for nurses. *Journal of Pediatric Nursing, 31*(1), 42-46.

Prevention of disease is a cornerstone of nursing care. Through our endeavors in research, teaching, and clinical care, nurses consistently seek to change the trajectory of disease development. The theoretical framework known as the Developmental Origins of Health and Disease (DOHaD) offers a new lens that shifts the current disease prevention paradigm upstream, encouraging intensified care of pregnant girls/women, neonates, and infants. This new focus parallels other emerging ecobiodevelopmental, life-course theories, which identify the long-term impact of early environments and stressors on the later risk of chronic adult diseases. Nurses have the potential to influence the health of multiple generations by incorporating DOHaD perspectives and interventions into their research and patient care. © 2016 Elsevier Inc.

Thilen, S. R., Wijeysondera, D. N., & Treggiari, M. M. (2016). Preoperative consultations. *Anesthesiology Clinics, 34*(1), 17-33.

Preoperative consultation is an important intervention that likely has most benefits for intermediate-risk to high-risk patients undergoing major surgery. Consultation rates are likely increasing and there is significant practice variation in the use of consultation. Consultations should be available within a well-organized and coordinated process of preoperative assessment. Preoperative consults should be accessible to anesthesia and surgical teams involved in the procedure and to the providers involved in postoperative care. The role of preoperative consultation should evolve as a rational approach and emerge as a value-based service. New payment methodologies are likely to facilitate appropriate use of this important resource.

Tudorica, A., Oh, K. Y., Chui, S. Y., Roy, N., Troxell, M. L., Naik, A., et al. (2016). Early prediction and evaluation of breast cancer response to neoadjuvant chemotherapy using quantitative DCE-MRI. *Translational Oncology, 9*(1), 8-17.

The purpose is to compare quantitative dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) metrics with imaging tumor size for early prediction of breast cancer response to neoadjuvant chemotherapy (NACT) and evaluation of residual cancer burden (RCB). Twenty-eight patients with 29 primary breast tumors underwent DCE-MRI exams before, after one cycle of, at

midpoint of, and after NACT. MRI tumor size in the longest diameter (LD) was measured according to the RECIST (Response Evaluation Criteria In Solid Tumors) guidelines. Pharmacokinetic analyses of DCE-MRI data were performed with the standard Tofts and Shutter-Speed models (TM and SSM). After one NACT cycle the percent changes of DCE-MRI parameters $K(\text{trans})$ (contrast agent plasma/interstitium transfer rate constant), v_e (extravascular and extracellular volume fraction), k_{ep} (intravasation rate constant), and SSM-unique tau (mean intracellular water lifetime) are good to excellent early predictors of pathologic complete response (pCR) vs. non-pCR, with univariate logistic regression C statistics value in the range of 0.804 to 0.967. v_e values after one cycle and at NACT midpoint are also good predictors of response, with C ranging 0.845 to 0.897. However, RECIST LD changes are poor predictors with $C = 0.609$ and 0.673 , respectively. Post-NACT $K(\text{trans})$, tau, and RECIST LD show statistically significant ($P < .05$) correlations with RCB. The performances of TM and SSM analyses for early prediction of response and RCB evaluation are comparable. In conclusion, quantitative DCE-MRI parameters are superior to imaging tumor size for early prediction of therapy response. Both TM and SSM analyses are effective for therapy response evaluation. However, the tau parameter derived only with SSM analysis allows the unique opportunity to potentially quantify therapy-induced changes in tumor energetic metabolism.

Ullsperger, J. M., Nigg, J. T., & Nikolas, M. A. (2016). Does child temperament play a role in the association between parenting practices and child attention Deficit/Hyperactivity disorder? *Journal of Abnormal Child Psychology*, *44*(1), 167-178.

Ineffective parenting practices may maintain or exacerbate attention deficit/hyperactivity disorder (ADHD) symptoms and shape subsequent development of disruptive behavior disorders (DBD's) in youth with ADHD. Recent theoretical models have suggested that parenting may exert effects on ADHD via its role in child temperament. The current study aimed to evaluate the indirect effects of parenting dimensions on child ADHD symptoms via child temperament. Youth ages 6–17 years ($N = 498$; 50.4 % ADHD, 55 % male) completed a multi-stage, multi-informant assessment that included parent, child, and teacher report measures of parenting practices, child temperament, and ADHD symptoms. Statistical models examined the direct and indirect effects of maternal and paternal involvement, poor supervision, and inconsistent discipline on inattention

and hyperactivity-impulsivity via child temperament and personality traits. Results indicated differential patterns of effect for negative and positive parenting dimensions. First, inconsistent discipline exerted indirect effects on both ADHD symptom dimensions via child conscientiousness, such that higher levels of inconsistency predicted lower levels of conscientiousness, which in turn, predicted greater ADHD symptomatology. Similarly, poor supervision also exerted indirect effects on inattention via child conscientiousness as well as significant indirect effects on hyperactivity-impulsivity via its impact on both child reactive control and conscientiousness. In contrast, primarily direct effects of positive parenting (i.e., involvement) on ADHD emerged. Secondary checks revealed that similar pathways may also emerge for comorbid disruptive behavior disorders. Current findings extend upon past work by examining how parenting practices influence child ADHD via within child mechanisms and provide support for multi-pathway models accounting for heterogeneity in the disorder. © 2015, Springer Science+Business Media New York.

Vacchi-Suzzi, C., Karimi, R., Kruse, D., Silbernagel, S. M., Levine, K. E., Rohlman, D. S., et al. (2016).

Low-level mercury, omega-3 index and neurobehavioral outcomes in an adult US coastal population. *European Journal of Nutrition*, 55(2), 699-711.

Background: Neurodevelopmental effects of omega-3 fatty acids and mercury from fish consumption have been characterized in children. In contrast, neurobehavioral outcomes associated with fish are not well studied in adults. Objective: This study of avid seafood consumers on Long Island (NY, USA) sought to define associations between mercury, seafood consumption, omega-3 fatty acids and neurobehavioral outcomes. Methods: A computer-based test system was used to assess neurobehavioral function. Blood total Hg (Hg) and omega-3 index were measured in 199 adult avid seafood eaters, who also completed the neurobehavioral assessment and an extensive food and fish frequency and demographic questionnaire. Results: For most of the outcomes considered, neither Hg nor omega-3 index was associated with neurobehavioral outcomes after adjustment for key confounding variables. Fish consumption, however, was associated with decreased odds of both self-reported fatigue (OR 0.85; 95 % CI 0.72, 1.01) and a constellation of neurologic symptoms (OR 0.79; 95 % CI 0.66, 0.96). Conclusions: Results from our study provide little evidence that omega-3 fatty acids or Hg is

associated with cognitive function in adult avid seafood consumers. Larger studies are needed to confirm our finding of associations between fish consumption and decreased self-reported fatigue and neurologic impairment. © 2015, Springer-Verlag Berlin Heidelberg.

Valent, A. M., Hall, E. S., & DeFranco, E. A. (2016). The influence of obesity on perinatal outcomes in pregnancies achieved with assisted reproductive technology: A population-based retrospective cohort study. *Obstetric Medicine, 9*(1), 34-39.

Objective: To determine the influence of obesity on neonatal outcomes of pregnancies resulting from assisted reproductive technology. Methods: Population-based retrospective cohort study of all non-anomalous, live births in Ohio from 2007 to 2011, comparing differences in the frequency of adverse neonatal outcomes of women who conceived with assisted reproductive technology versus spontaneously conceived pregnancies and stratified by obesity status. Primary outcome was a composite of neonatal morbidities defined as ≥ 1 of the following: neonatal death, Apgar score of 7 at 5 min, assisted ventilation, neonatal intensive care unit admission, or transport to a tertiary care facility. Results: Rates of adverse neonatal outcomes were significantly higher for assisted reproductive technology pregnancies than spontaneously conceived neonates; non-obese 25% versus 8% and obese 27% versus 10%, $p < 0.001$. Assisted reproductive technology was associated with a similar increased risk for adverse outcomes in both obese (adjusted odds ratio (aOR): 1.33, 95% confidence interval (CI): 1.11–1.59) and non-obese women (aOR: 1.34, 95% CI: 1.18–1.51) even after adjustment for coexisting risk factors. This increased risk was driven by higher preterm births in assisted reproductive technology pregnancies; obese (aOR: 1.06, 95% CI: 0.86–1.31) and non-obese (aOR: 1.15, 95% CI: 1.00–1.32). Discussion: Assisted reproductive technology is associated with a higher risk of adverse neonatal outcomes. Obesity does not appear to adversely modify perinatal risks associated with assisted reproductive technology. © 2016, © The Author(s) 2016.

Varney, S. D., Betts, C. B., Zheng, R., Wu, L., Hinz, B., Zhou, J., et al. (2016). Hic-5 is required for myofibroblast differentiation by regulating mechanically dependent MRTF-A nuclear accumulation. *Journal of Cell Science, 129*(4), 774-787.

How mechanical cues from the extracellular environment are translated biochemically to

modulate the effects of TGF- β on myofibroblast differentiation remains a crucial area of investigation. We report here that the focal adhesion protein, Hic-5 (also known as TGFB111), is required for the mechanically dependent generation of stress fibers in response to TGF- β . Successful generation of stress fibers promotes the nuclear localization of the transcriptional co-factor MRTF-A (also known as MKL1), and this correlates with the mechanically dependent induction of α -smooth muscle actin (α -SMA) and Hic-5 in response to TGF- β . As a consequence of regulating stress fiber assembly, Hic-5 is required for the nuclear accumulation of MRTF-A and the induction of α -SMA as well as cellular contractility, suggesting a crucial role for Hic-5 in myofibroblast differentiation. Indeed, the expression of Hic-5 was transient in acute wounds and persistent in pathogenic scars, and Hic-5 colocalized with α -SMA expression in vivo. Taken together, these data suggest that a mechanically dependent feed-forward loop, elaborated by the reciprocal regulation of MRTF-A localization by Hic-5 and Hic-5 expression by MRTF-A, plays a crucial role in myofibroblast differentiation in response to TGF- β . © 2016. Published by The Company of Biologists Ltd.

Veltri, L., Kaakinen, J. R., Shillam, C., Arwood, E., & Bell, K. (2016). Controlled postpartum-newborn simulation with objective evaluation exchanged for clinical learning. *Clinical Simulation in Nursing*, 12(5), 177-186.

Background: Simulation offers educators a way to replicate traditional clinical experiences in a controlled, safe environment. Simulated training bolsters nursing students' confidence, and nurse educators find simulation delivers measurable performance improvements. Method:

Undergraduate nursing students' performance and learning in a simulated setting was compared with a traditional clinical setting. Results: Findings revealed no significant differences in ability to demonstrate competent assessment skills, determine appropriate interventions, and think critically between students in a traditional pediatric clinical experience with postpartum-newborn simulations, compared with students in a traditional maternal-newborn clinical plus the same simulations. Differences between high- and low-performing student's performance in skills were evaluated beyond simple observation based on a standardized simulation evaluation tool.

Conclusions: These results support replacing traditional clinical experiences with simulation and provide support for objective evaluation benchmarking clinical reasoning capabilities beyond the

"pass/fail" evaluation of student competency. © 2016 International Nursing Association for Clinical Simulation and Learning.

Venkataramani, S., & Taylor, W. R. (2016). Synaptic mechanisms generating orientation selectivity in the on pathway of the rabbit retina. *Journal of Neuroscience*, *36*(11), 3336-3349.

Neurons that signal the orientation of edges within the visual field have been widely studied in primary visual cortex. Much less is known about the mechanisms of orientation selectivity that arise earlier in the visual stream. Here we examine the synaptic and morphological properties of a subtype of orientation-selective ganglion cell in the rabbit retina. The receptive field has an excitatory ON center, flanked by excitatory OFF regions, a structure similar to simple cell receptive fields in primary visual cortex. Examination of the light-evoked postsynaptic currents in these ON-type orientation-selective ganglion cells (ON-OSGCs) reveals that synaptic input is mediated almost exclusively through the ON pathway. Orientation selectivity is generated by larger excitation for preferred relative to orthogonal stimuli, and conversely larger inhibition for orthogonal relative to preferred stimuli. Excitatory orientation selectivity arises in part from the morphology of the dendritic arbors. Blocking GABA_A receptors reduces orientation selectivity of the inhibitory synaptic inputs and the spiking responses. Negative contrast stimuli in the flanking regions produce orientation-selective excitation in part by disinhibition of a tonic NMDA receptor-mediated input arising from ON bipolar cells. Comparison with earlier studies of OFF-type OSGCs indicates that diverse synaptic circuits have evolved in the retina to detect the orientation of edges in the visual input. © 2016 the authors.

Vetto, J. T. (2016). Change, organizations, and good scouts. *American Journal of Surgery*,

Viola, S., Traer, E., Huan, J., Hornick, N. I., Tyner, J. W., Agarwal, A., et al. (2016). Alterations in acute myeloid leukaemia bone marrow stromal cell exosome content coincide with gains in tyrosine kinase inhibitor resistance. *British Journal of Haematology*, *172*(6), 983-986.

Vita, R., Vasilevsky, N., Bandrowski, A., Haendel, M., Sette, A., & Peters, B. (2016). Reproducibility and conflicts in immune epitope data. *Immunology*, *147*(3), 349-354.

The Immune Epitope Database is uniquely positioned to assess the body of research related to

immune epitopes, we have manually curated all such published data. Thus, we are able to make observations on the state of these fields of research, as well as aggregate the individual data points to present a clearer picture of the immune response to specific antigens in all studied hosts. Additionally, we are able to identify where conflicts in the literature exist and where publications fall short in terms of identifiable methods and in reproducibility. Here we present guidelines to improve the quality of immune epitope data, which will benefit journals and researchers alike. © 2016 John Wiley & Sons Ltd.

Voss, H. C. (2016). Preceptors'™ experience of nursing service-learning projects. *Journal of Nursing Education, 55*(3), 150-154.

Background: Service-learning is a teaching"learning strategy in higher education that provides hands-on experiences in authentic clinical environments. Mutual decision making, shared goals, reciprocity, and tangible benefits to organizations and the people they serve are hallmarks of service-learning. However, the literature is sparse pertaining to preceptor experiences with service-learning projects, the extent of reciprocity, or the projects"™ impact on those who received the service. Method: A small phenomenological study was conducted to better understand the experiences of four community-based health professionals who worked with nursing students on service-learning projects. Results: Four themes emerged from face-to-face interviews and written reflections: (a) reciprocity among preceptor, clinical faculty, and student, (b) intentional planning and project clarity, (c) meaningful and authentic experience, and (d) valued and beneficial contributions that addressed a need. Conclusion: Insight gained from the experiences of the four preceptors in this study suggest that through careful planning and reciprocity, service-learning™ can have a positive impact on community-based organizations and the people they serve. © SLACK Incorporated.

Ward, M. M., Deodhar, A., Reveille, J. D., & Caplan, L. (2016). Response to "comment on the recommendations by ward et al for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis" by akkoc and khan. *Arthritis Care & Research,*

Warren, J. B., Hamilton, A., & Ruge, B. (2015). Q what's the best way to predict the success of a trial of labor after a previous C-section? *Journal of Family Practice, 64*(12), E3-E7.

Watson, J. J. J., Moren, A., Diggs, B., Houser, B., Eastes, L., Brand, D., et al. (2016). A statewide teleradiology system reduces radiation exposure and charges in transferred trauma patients. *American Journal of Surgery*,

Background: Trauma transfer patients routinely undergo repeat imaging because of inefficiencies within the radiology system. In 2009, the virtual private network (VPN) telemedicine system was adopted throughout Oregon allowing virtual image transfer between hospitals. The startup cost was a nominal \$3,000 per hospital. Methods: A retrospective review from 2007 to 2012 included 400 randomly selected adult trauma transfer patients based on a power analysis (200 pre/200 post). The primary outcome evaluated was reduction in repeat computed tomography (CT) scans. Secondary outcomes included cost savings, emergency department (ED) length of stay (LOS), and spared radiation. All data were analyzed using Mann-Whitney U and chi-square tests. P less than .05 indicated significance. Spared radiation was calculated as a weighted average per body region, and savings was calculated using charges obtained from Oregon Health and Science University radiology current procedural terminology codes. Results: Four-hundred patients were included. Injury Severity Score, age, ED and overall LOS, mortality, trauma type, and gender were not statistically different between groups. The percentage of patients with repeat CT scans decreased after VPN implementation: CT abdomen (13.2% vs 2.8%, $P < .01$) and cervical spine (34.4% vs 18.2%, $P < .01$). Post-VPN, the total charges saved in 2012 for trauma transfer patients was \$333,500, whereas the average radiation dose spared per person was 1.8 mSV. Length of stay in the ED for patients with Injury Severity Score less than 15 transferring to the ICU was decreased ($P < .05$). Conclusions: Implementation of a statewide teleradiology network resulted in fewer total repeat CT scans, significant savings, decrease in radiation exposure, and decreased LOS in the ED for patients with less complex injuries. The potential for health care savings by widespread adoption of a VPN is significant. © 2016 Elsevier Inc.

Weddle, M. (2016). Bioethicist or philosopher king? *American Journal of Bioethics*, 16(4), 31-33.

Wiegand, N., Hart, K. D., Kelley, K., Lu, K. C., Herzig, D. O., Mitin, T., et al. (2016). HIV positivity and anal cancer outcomes: A single-center experience. *American Journal of Surgery*,
BACKGROUND: Anal cancer remains common among human immunodeficiency virus (HIV)

patients. Chemoradiation has had mixed results. We evaluated outcome differences by HIV status. METHODS: We retrospectively analyzed 14 HIV+ and 72 HIV- anal cancer patients (2000 to 2013). Outcomes included chemoradiation tolerance, recurrence, and survival. RESULTS: HIV+ patients were more often male (100% vs 38%, $P < .001$) but diagnosed at similar stages ($P = .49$). They were less likely to receive traditional chemotherapy (36% vs 86%, $P < .001$). Recurrence ($P = .55$) and survival time ($P = .48$) were similar across groups. HIV+ patients had similar colostomy-free survival ($P = .053$). Receipt of 5-fluorouracil/mitomycin C (MMC) chemotherapy predicted recurrence-free and overall survival (Hazard ratios .278, .32). HIV status did not worsen recurrence ($P = .71$) or survival ($P = .57$). CONCLUSIONS: HIV+ patients received more non-MMC-based chemoradiation but had equivalent colostomy-free, recurrence, and overall survival. Use of 5-fluorouracil/MMC chemotherapy increased after 2008.

Wiggs, K., Elmore, A. L., Nigg, J. T., & Nikolas, M. A. (2016). Pre- and perinatal risk for attention-deficit hyperactivity disorder: Does neuropsychological weakness explain the link? *Journal of Abnormal Child Psychology*,

Etiological investigations of attention-deficit hyperactivity disorder (ADHD) and disruptive behavior problems support multiple causal pathways, including involvement of pre- and perinatal risk factors. Because these risks occur early in life, well before observable ADHD and externalizing symptoms emerge, the relation between risk and symptoms may be mediated by neurodevelopmental effects that manifest later in neuropsychological functioning. However, potential dissociable effects of pre/perinatal risk elements on ADHD and familial confounds must also be considered to test alternative hypotheses. 498 youth aged 6-17 years (55.0 % male) completed a multi-stage, multi-informant assessment including parent and teacher symptom reports of symptoms and parent ratings of pre/perinatal health risk indicators. Youth completed a neuropsychological testing battery. Multiple mediation models examined direct effects of pre- and perinatal health risk on ADHD and other disruptive behavior disorder symptoms and indirect effects via neuropsychological functioning. Parental ADHD symptoms and externalizing status was covaried to control for potential familial effects. Effects of prenatal substance exposure on inattention were mediated by memory span and temporal processing deficits. Further, effects of perinatal health risk on inattention, hyperactivity-impulsivity, and ODD were mediated by deficits

in response variability and temporal processing. Further, maternal health risks during pregnancy appeared to exert direct rather than indirect effects on outcomes. Results suggest that after controlling for familial relatedness of ADHD between parent and child, early developmental health risks may influence ADHD via effects on neuropsychological processes underpinning the disorder.

Wormald, P. J., Hoseman, W., Callejas, C., Weber, R. K., Kennedy, D. W., Citardi, M. J., et al. (2016).

The international frontal sinus anatomy classification (IFAC) and classification of the extent of endoscopic frontal sinus surgery (EFSS). *International Forum of Allergy & Rhinology*,

The frontal recess and frontal sinus anatomy can vary from simple to complex. The variations in the anatomy of the frontal recess and frontal sinus are considerable but almost all variations can be classified if the various cell patterns are analyzed. This consensus document was developed to improve the ability of the surgeon to understand these possible variations, plan the surgery, and communicate these complexities when teaching or reporting outcomes. Once the surgeon understands the anatomical pattern of the frontal sinus and recess cells, the extent of surgery can be planned. This document presents a classification of the extent of surgery based on the anatomical classification.

Xuan, C., Tian, Q. -, Li, H., Zhang, B. -, He, G. -, & Lun, L. -. (2016). Levels of asymmetric

dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, and risk of coronary artery disease: A meta-analysis based on 4713 participants. *European Journal of Preventive Cardiology*, 23(5), 502-510.

Background Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of endothelial nitric oxide synthase by competing with L-arginine. As a result, the expression of nitric oxide decreases and endothelial dysfunction occurs. Studies have evaluated the association between the serum ADMA level and risk of coronary artery disease. However, conflicting results have been obtained. Methods Pubmed, Web of Science, Embase, Ovid, Cochrane databases were searched to identify eligible studies published in English until December 2014. Association was assessed on the basis of weighted mean differences (WMD) with 95% confidence intervals (CIs). Publication bias was analysed using Begg's and Egger's tests. Sensitivity analysis was performed to evaluate result stability. Results A total of 16 case-control studies with 2939 patients and 1774 controls were

included in the meta-analysis. Pooled result indicated that patients with coronary artery disease yielded a higher ADMA level than healthy controls (WMD: 0.248, 95% CI: 0.156-0.340; $p = 1.16 \times 10^{-7}$). Sensitivity analysis suggested that our meta-analysis result was stable. Subgroup analysis found a similar pattern in patients with myocardial infarction (WMD: 0.397, 95% CI: 0.112-0.683; $p = 0.0106$), stable angina pectoris (WMD: 0.197, 95% CI: 0.031-0.364; $p = 0.02$) and unstable angina pectoris (WMD: 0.857, 95% CI: 0.293-1.420; $p = 0.003$). Conclusions Meta-analysis results indicated that an increased ADMA level is associated with an increased risk of coronary artery disease. © The European Society of Cardiology 2015.

Yankeelov, T. E., Mankoff, D. A., Schwartz, L. H., Lieberman, F. S., Buatti, J. M., Mountz, J. M., et al. (2016). Quantitative imaging in cancer clinical trials. *Clinical Cancer Research*, 22(2), 284-290.

As anticancer therapies designed to target specific molecular pathways have been developed, it has become critical to develop methods to assess the response induced by such agents. Although traditional, anatomic CT, and MRI examinations are useful in many settings, increasing evidence suggests that these methods cannot answer the fundamental biologic and physiologic questions essential for assessment and, eventually, prediction of treatment response in the clinical trial setting, especially in the critical period soon after treatment is initiated. To optimally apply advances in quantitative imaging methods to trials of targeted cancer therapy, new infrastructure improvements are needed that incorporate these emerging techniques into the settings where they are most likely to have impact. In this review, we first elucidate the needs for therapeutic response assessment in the era of molecularly targeted therapy and describe how quantitative imaging can most effectively provide scientifically and clinically relevant data. We then describe the tools and methods required to apply quantitative imaging and provide concrete examples of work making these advances practically available for routine application in clinical trials. We conclude by proposing strategies to surmount barriers to wider incorporation of these quantitative imaging methods into clinical trials and, eventually, clinical practice. Our goal is to encourage and guide the oncology community to deploy standardized quantitative imaging techniques in clinical trials to further personalize care for cancer patients and to provide a more efficient path for the development of improved targeted therapies. © 2016 American Association for Cancer Research.

Yap, F. C., Weber, D. S., Taylor, M. S., Townsley, M. I., Comer, B. S., Maylie, J., et al. (2016).

Endothelial SK3 channel-associated Ca²⁺ microdomains modulate blood pressure. *American Journal of Physiology. Heart and Circulatory Physiology*, , ajpheart.00787.2015.

Activation of vascular endothelial small- (KCa_{2.3}, SK3) or intermediate- (KCa_{3.1}, IK1) conductance Ca²⁺-activated potassium channels induces vasorelaxation via an endothelium-derived hyperpolarization (EDH) pathway. Although the activation of SK3 and IK1 channels converges on EDH, their subcellular effects on signal transduction are different and not completely clear. In this study a novel endothelium-specific SK3 knockout (SK3^{-/-}) mouse model was utilized to specifically examine the contribution of SK3 channels to mesenteric artery vasorelaxation, endothelial Ca²⁺ dynamics, and blood pressure. The absence of SK3 expression was confirmed using real-time qPCR and western blot analysis. Functional studies showed impaired EDH-mediated vasorelaxation in SK3^{-/-} small mesenteric arteries. Immunostaining results from SK3^{-/-} vessels confirmed the absence of SK3 and further showed altered distribution of TRPV4 (transient receptor potential channels, type 4). Electrophysiological recordings showed a lack of SK3 channel activity, while TRPV4-IK1 channel coupling remained intact in SK3^{-/-} endothelial cells. Moreover, Ca²⁺ imaging studies in SK3^{-/-} endothelium showed increased Ca²⁺ transients with reduced amplitude and duration under basal conditions. Importantly, SK3^{-/-} endothelium lacked a distinct type of Ca²⁺ dynamic that is sensitive to TRPV4 activation. Blood pressure measurements showed that the SK3^{-/-} mice were hypertensive, and the blood pressure increase was further enhanced during the 12 hr dark-cycle when animals are most active. Taken together, our results reveal a previously unappreciated SK3 signaling microdomain that modulates endothelial Ca²⁺ dynamics, vascular tone, and blood pressure.

Ye, J. C., Thomas, C. R., J., Braunstein, S., Hirsch, A. E., Gunther, J. R., & Golden, D. W. (2016). In regard to ahmed et al. *International Journal of Radiation Oncology Biology Physics*, 94(5), 1221-1222.

Yee, J. L., Vanderford, T. H., Didier, E. S., Gray, S., Lewis, A., Roberts, J., et al. (2016). Specific pathogen free macaque colonies: A review of principles and recent advances for viral testing and colony management. *Journal of Medical Primatology*, 45(2), 55-78.

Specific pathogen free (SPF) macaques provide valuable animal models for biomedical research. In 1989, the National Center for Research Resources [now Office of Research Infrastructure Programs (ORIP)] of the National Institutes of Health initiated experimental research contracts to establish and maintain SPF colonies. The derivation and maintenance of SPF macaque colonies is a complex undertaking requiring knowledge of the biology of the agents for exclusion and normal physiology and behavior of macaques, application of the latest diagnostic technology, facility management, and animal husbandry. This review provides information on the biology of the four viral agents targeted for exclusion in ORIP SPF macaque colonies, describes current state-of-the-art viral diagnostic algorithms, presents data from proficiency testing of diagnostic assays between laboratories at institutions participating in the ORIP SPF program, and outlines management strategies for maintaining the integrity of SPF colonies using results of diagnostic testing as a guide to decision making.

Yokogawa, H., Tang, M., Li, Y., Liu, L., Chamberlain, W., & Huang, D. (2016). Deep laser-assisted lamellar anterior keratoplasty with microkeratome-cut grafts. *Cornea*,

PURPOSE:: The goals of this laboratory study were to evaluate the interface quality in laser-assisted lamellar anterior keratoplasty (LALAK) with microkeratome-cut grafts and achieve good graft–host apposition. METHODS:: Simulated LALAK surgeries were performed on 6 pairs of eye-bank corneoscleral discs. Anterior lamellar grafts were pre-cut with microkeratomes. Deep femtosecond (FS) laser cuts were performed on host corneas followed by excimer laser smoothing. Different parameters of FS laser cuts and excimer laser smoothing were tested. Optical coherence tomography was used to measure corneal pachymetry and evaluate graft–host apposition. The interface quality was quantified in a masked fashion using a 5-point scale based on scanning electron microscopy images. RESULTS:: Deep FS laser cuts at 226 to 380 μm resulted in visible ridges on the host bed. Excimer laser smoothing with a central ablation depth of 29 μm and saline as a smoothing agent did not adequately reduce ridges (score = 4.0). Deeper excimer laser ablation of 58 μm and Optisol-GS as a smoothing agent smoothed ridges to an acceptable level (score = 2.1). Same sizing of the graft and host cut diameters with an approximately 50- μm deeper host side cut relative to the central graft thickness provided the best graft–host fit. CONCLUSIONS:: Deep excimer laser ablation with a viscous smoothing agent

was needed to remove ridges after deep FS lamellar cuts. The host side cut should be deep enough to accommodate thicker graft peripheral thickness compared with the center. This LALAK design provides smooth lamellar interfaces, moderately thick grafts, and good graft–host fits.

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Young, J. -. H., Logan, B. R., Wu, J., Wingard, J. R., Weisdorf, D. J., Mudrick, C., et al. (2016).

Infections after transplantation of bone marrow or peripheral blood stem cells from unrelated donors. *Biology of Blood and Marrow Transplantation*, 22(2), 359-370.

Infection is a major complication of hematopoietic cell transplantation. Prolonged neutropenia and graft-versus-host disease are the 2 major complications with an associated risk for infection, and these complications differ according to the graft source. A phase 3, multicenter, randomized trial (Blood and Marrow Transplant Clinical Trials Network [BMT CTN] 0201) of transplantation of bone marrow (BM) versus peripheral blood stem cells (PBSC) from unrelated donors showed no significant differences in 2-year survival between these graft sources. In an effort to provide data regarding whether BM or PBSC could be used as a preferential graft source for transplantation, we report a detailed analysis of the infectious complications for 2 years after transplantation from the BMT CTN 0201 trial. A total of 499 patients in this study had full audits of infection data. A total of 1347 infection episodes of moderate or greater severity were documented in 384 (77%) patients; 201 of 249 (81%) of the evaluable patients had received a BM graft and 183 of 250 (73%) had received a PBSC graft. Of 1347 infection episodes, 373 were severe and 123 were life-threatening and/or fatal; 710 (53%) of these episodes occurred on the BM arm and 637 (47%) on the PBSC arm, resulting in a 2-year cumulative incidence 84.7% (95% confidence interval [CI], 79.6 to 89.8) for BM versus 79.7% (95% CI, 73.9 to 85.5) for PBSC, $P = 0.13$. The majority of these episodes, 810 (60%), were due to bacteria, with a 2-year cumulative incidence of 72.1% and 62.9% in BM versus PBSC recipients, respectively ($P = 0.03$). The cumulative incidence of bloodstream bacterial infections during the first 100 days was 44.8% (95% CI, 38.5 to 51.1) for BM versus 35.0% (95% CI, 28.9 to 41.1) for PBSC ($P = 0.27$). The total infection density (number of infection events/100 patient days at risk) was .67 for BM and .60 for PBSC. The overall infection density for bacterial infections was .4 in both arms; for viral infections, it was .2 in both arms; and for fungal/parasitic infections, it was .04 and .05 for BM and PBSC,

respectively. The cumulative incidence of infection before engraftment was 47.9% (95% CI, 41.5 to 53.9) for BM versus 32.8% (95% CI, 27.1 to 38.7) for PBSC (P =002), possibly related to quicker neutrophil engraftment using PBSC. Infections remain frequent after unrelated donor hematopoietic cell transplantation, particularly after BM grafts. © 2016 American Society for Blood and Marrow Transplantation.

Young, J. I., Mongoue-Tchokote, S., Wieghard, N., Mori, M., Vaccaro, G. M., Sheppard, B. C., et al. (2016). Treatment and survival of small-bowel adenocarcinoma in the united states: A comparison with colon cancer. *Diseases of the Colon and Rectum*, 59(4), 306-315.

BACKGROUND: Small-bowel adenocarcinoma is rare and fatal. Because of data paucity, there is a tendency to extrapolate treatment from colon cancer, particularly in the adjuvant setting.

OBJECTIVE: The purpose of this study was to evaluate the current surgical and adjuvant treatments of small-bowel adenocarcinoma and compare with colon cancer. DESIGN: This was a retrospective cohort study. SETTINGS: The linked Surveillance, Epidemiology, and End Results and Medicare database was used at a tertiary referral hospital. PATIENTS: Patients with small-bowel adenocarcinoma and colon cancer identified from 1992 to 2010, using International Classification of Diseases for Oncology, 3 Revision, site, behavior, and histology codes were included. MAIN OUTCOME MEASURES: Overall survival and cancer-specific survival were estimated using the Kaplan-Meier method and competing risk analysis. RESULTS: A total of 2123 patients with small-bowel adenocarcinoma and 248,862 patients with colon cancer were identified. Five-year overall survival rates for patients with small-bowel adenocarcinoma and colon cancer were 34.9% and 51.5% (p < 0.0001). A total of 1550 patients with small-bowel adenocarcinoma (73.0%) underwent surgery, compared with 177,017 patients with colon cancer (71.1%). The proportion of patients who received chemotherapy was similar, at 21.3% for small bowel and 20.0% for colon. In contrast to colon cancer, chemotherapy did not improve overall or cancer-specific survival for patients with small-bowel adenocarcinoma, regardless of stage. Predictors of poor survival for small-bowel adenocarcinoma on multivariate analysis included advanced age, black race, advanced stage, poor tumor differentiation, high comorbidity index, and distal location. Chemotherapy did not confer additional survival benefit compared with surgery alone (HR, 1.04 (95% CI, 0.90-1.22)). LIMITATIONS: This was a retrospective review.

The reliance on Medicare data limited granularity and may have affected the generalizability of the results. CONCLUSIONS: The prognosis for small-bowel adenocarcinoma is worse than that for colon cancer, and only surgery improves survival. In contrast to colon cancer, a survival benefit from current chemotherapy regimens for small-bowel adenocarcinoma is not seen, suggesting that it may be overused and needs more rigorous study.

Yu, Y., Chen, J., Leary, C. I., Shugard, E., & Yom, S. S. (2016). Split-field vs extended-field intensity-modulated radiation therapy plans for oropharyngeal cancer: Which spares the larynx? which spares the thyroid? *Medical Dosimetry : Official Journal of the American Association of Medical Dosimetrists*,

Radiation of the low neck can be accomplished using split-field intensity-modulated radiation therapy (sf-IMRT) or extended-field intensity-modulated radiation therapy (ef-IMRT). We evaluated the effect of these treatment choices on target coverage and thyroid and larynx doses. Using data from 14 patients with cancers of the oropharynx, we compared the following 3 strategies for radiating the low neck: (1) extended-field IMRT, (2) traditional split-field IMRT with an initial cord-junction block to 40Gy, followed by a full-cord block to 50Gy, and (3) split-field IMRT with a full-cord block to 50Gy. Patients were planned using each of these 3 techniques. To facilitate comparison, extended-field plans were normalized to deliver 50Gy to 95% of the neck volume. Target coverage was assessed using the dose to 95% of the neck volume (D95). Mean thyroid and larynx doses were computed. Extended-field IMRT was used as the reference arm; the mean larynx dose was 25.7 +/- 7.4Gy, and the mean thyroid dose was 28.6 +/- 2.4Gy. Split-field IMRT with 2-step blocking reduced laryngeal dose (mean larynx dose 15.2 +/- 5.1Gy) at the cost of a moderate reduction in target coverage (D95 41.4 +/- 14Gy) and much higher thyroid dose (mean thyroid dose 44.7 +/- 3.7Gy). Split-field IMRT with initial full-cord block resulted in greater laryngeal sparing (mean larynx dose 14.2 +/- 5.1Gy) and only a moderately higher thyroid dose (mean thyroid dose 31 +/- 8Gy) but resulted in a significant reduction in target coverage (D95 34.4 +/- 15Gy). Extended-field IMRT comprehensively covers the low neck and achieves acceptable thyroid and laryngeal sparing. Split-field IMRT with a full-cord block reduces laryngeal doses to less than 20Gy and spares the thyroid, at the cost of substantially reduced

coverage of the low neck. Traditional 2-step split-field IMRT similarly reduces the laryngeal dose but also reduces low-neck coverage and delivers very high doses to the thyroid.

Yun, H., Yang, S., Chen, L., Xie, F., Winthrop, K., Baddley, J. W., et al. (2016). Risk of herpes zoster in auto-immune and inflammatory diseases: Implications for vaccination. *Arthritis & Rheumatology (Hoboken, N.J.)*,

Background The herpes zoster (HZ) vaccine is recommended for adults age ≥ 60 years without weakened immune systems in the U.S. It is unclear how the risk of HZ varies according to age and disease conditions for younger patients with autoimmune or inflammatory (AI) diseases. We evaluated the age-stratified incidence of HZ associated with AI diseases compared to adults recommended for vaccination by the CDC. Methods Using linked commercial and governmentally-insured patients (2007-2010), we assembled seven AI cohorts: systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), gout and two comparison cohorts: diabetes and patients without AI and diabetic conditions. We identified HZ using diagnostic codes. Age-specific incidence rates (IR) were calculated and compared with the IR in patients aged 60-69 and without AI and diabetic conditions. Results We identified 8,395 SLE, 7,916 IBD, 50,646 RA, 2,629 PsA, 4,299 PsO, 1,019 AS, 58,934 gout, 214,631 diabetes and 330,727 enrollment periods without AI and diabetic conditions. Highest to lowest, the IRs ranged from 19.9 per 1,000 yrs for SLE cohort to 6.8 for gout cohort, versus 5.3 in patients without AI and diabetic conditions. The age-specific IRs of HZ for RA and SLE patients aged ≥ 40 were 1.5-2 times greater than those observed in healthy adults for whom the vaccine is currently recommended (8.5/1000).

CONCLUSIONS: SLE, IBD and RA are associated with higher risks of HZ compared to older adults recommended for vaccination, suggesting that individuals with these conditions as young as age 40 could potentially benefit from vaccination. This article is protected by copyright. All rights reserved.

Zerbe, K. (2016). Psychodynamic issues in the treatment of binge eating: Working with shame, secrets, no-entry, and false body defenses. *Clinical Social Work Journal*, 44(1), 8-17.

Two clinical moments from patients in treatment for Binge Eating Disorder (DSM 5) are described

where a manifest problem with body image difficulty was initially denied. Each patient entered treatment with the desire to lose weight as well as gain a fuller understanding of self and mastery over addictive eating patterns that caused considerable psychological anguish. An integrated treatment matrix of practical, contemporary psychodynamic interventions and more behavioral, experiential and supportive tools allowed each patient to uncover and work through heretofore split off aspects of their bodily selves. Defense mechanisms such as 'no entry' fantasies and 'the false body' that have recently been described in the analytic literature are applied in formulating each case example. The author underscores how therapists must probe for secrets in the personal and family history that are 'hidden, but in plain view' and pursue them in order for the patient to embrace a more coherent, true sense of her/his bodily self. These secrets often contain a less conscious rationale for treating the body poorly and perpetuating hated, shameful and derogatory aspects of body image that may become externalized onto the therapist. These externalizations can further complicate countertransference reactions that must be acknowledged and worked through by the therapist in personal or self-analysis. © 2015, Springer Science+Business Media New York.

Zhang, L., Zheng, A., Nie, H., Bhavsar, K. V., Xu, Y., Sliney, D. H., et al. (2016). Laser-induced photic injury phenocopies macular dystrophy. *Ophthalmic Genetics*, 37(1), 59-67.

OBJECTIVE: To describe the phenotypes associated with laser-induced retinal damage in children.

METHODS: Five patients with maculopathy and reduced visual acuity associated with laser pointer use were evaluated. Best-corrected visual acuity, retinal structure, and function were monitored with color fundus, infrared (IR), and red-free images, fundus autofluorescence (AF), spectral domain-optical coherence tomography (SD-OCT), and full-field electroretinography (ERG).

RESULTS: All five laser pointer injury patients had retinal lesions resembling a macular dystrophy (one bilateral and four unilateral). These lesions were irregular in shape but all had a characteristic dendritic appearance with linear streaks radiating from the lesion. Photoreceptor damage was present in all patients, but serial OCT monitoring showed that subsequent photoreceptor recovery occurred over time in the eyes of at least four patients. One patient also had bilateral pigment epithelial detachments (PED). Both hyper- and hypoautofluorescence were observed in the laser damage area. **CONCLUSIONS:** In general, OCT and IR images are quite

useful to diagnose laser damage, but AF is not as sensitive. Laser pointer damage in children can occasionally be misdiagnosed as a macular dystrophy disease, but the distinctive lesions and OCT features are helpful for differentiating laser damage from other conditions.

Zhang, X., Loewen, N., Tan, O., Greenfield, D. S., Schuman, J. S., Varma, R., et al. (2016). Predicting development of glaucomatous visual field conversion using baseline fourier-domain optical coherence tomography. *American Journal of Ophthalmology*, 163, 29-37.

Purpose To predict the development of glaucomatous visual field (VF) defects using Fourier-domain optical coherence tomography (FD OCT) measurements at baseline visit. **Design** Multicenter longitudinal observational study. **Participants** Glaucoma suspects and preperimetric glaucoma participants in the Advanced Imaging for Glaucoma Study. **Methods** The optic disc, peripapillary retinal nerve fiber layer (NFL), and macular ganglion cell complex (GCC) were imaged with FD OCT. VF was assessed every 6 months. Conversion to perimetric glaucoma was defined by VF pattern standard deviation (PSD) or glaucoma hemifield test (GHT) outside normal limits on 3 consecutive tests. Hazard ratios were calculated with the Cox proportional hazard model. **Predictive accuracy** was measured by the area under the receiver operating characteristic curve (AUC). **Results** Of 513 eyes (309 participants), 55 eyes (46 participants) experienced VF conversion during 41 ± 23 months of follow-up. Significant ($P < .05$, Cox regression) FD OCT risk factors included all GCC, NFL, and disc variables, except for horizontal cup-to-disc ratio. GCC focal loss volume (FLV) was the best single predictor of conversion (AUC = 0.753, $P < .001$ for test against AUC = 0.5). Those with borderline or abnormal GCC-FLV had a 4-fold increase in conversion risk after 6 years (Kaplan-Meier). Optimal prediction of conversion was obtained using the glaucoma composite conversion index (GCCCI) based on a multivariate Cox regression model that included GCC-FLV, inferior NFL quadrant thickness, age, and VF PSD. GCCCI significantly improved predictive accuracy (AUC = 0.783) over any single variable ($P = .04$). **Conclusions** Reductions in NFL and GCC thickness can predict the development of glaucomatous VF loss in glaucoma suspects and preperimetric glaucoma patients. © 2016 Elsevier Inc. All rights reserved.