

## References

Abdala, A. P., Toward, M. A., Dutschmann, M., Bissonnette, J. M., & Paton, J. F. (2015). Deficiency of GABAergic synaptic inhibition in the kolliker-fuse area underlies respiratory dysrhythmia in a mouse model of rett syndrome. *The Journal of Physiology*,

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

Abola, M. V., & Prasad, V. (2015). The use of superlatives in cancer research. *JAMA Oncology*, , 1-2.

Ahmadi, H., & Lee, C. T. (2015). Health-related quality of life with urinary diversion. *Current Opinion in Urology*, 25(6), 562-569.

Purpose of review Patients who undergo radical cystectomy and urinary diversion experience a

lengthy period of postoperative recovery from physical, functional, social, and emotional challenges that greatly impact health-related quality of life (HRQoL). These changes affect nearly all patients and must be reviewed in detail as part of the preoperative consultation. However, quantifying a patient's risk for altered HRQoL is imprecise, thus complicating the choice for urinary diversion. Recent findings A recent prospective study observed improved global health status and physical, role, and social functioning in patients treated with orthotopic neobladder diversion compared with patients treated with ileal conduit diversion. In contrast, robotic-assisted radical cystectomy does not improve patient quality of life (QoL) over open radical cystectomy within the first year of surgery. Enhanced recovery protocols improve immediate postoperative QoL but their effect on long-term QoL is uncertain. Summary There is still a significant lack of understanding about the QoL between various types of urinary diversions. Recent and ongoing prospective randomized trials in the radical cystectomy population may shed light on urinary diversion-specific function and related effects on HRQoL. Ultimately, well designed, large multicenter prospective-controlled trials comparing functional, social, and emotional outcomes of continent and incontinent urinary diversion are still needed. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Ahmadi, H., Montie, J. E., Weizer, A. Z., Morgan, T., Montgomery, J. S., & Lee, C. T. (2015). Patient psoas muscle mass as a predictor of complications and survival after radical cystectomy. *Current Urology Reports*, 16(11), 79-015-0548-0.

As a treatment for high-risk bladder cancer, radical cystectomy (RC) remains a highly morbid operation with complication rates of 40-60 % and mortality rates as high as 9 % in the first 90 days after surgery (Aziz et al., *Eur Urol* 66(1):156-163, 2014; Shabsigh et al., *Eur Urol* 55(1):164-174, 2009). Many patients suffer from a failure-to-thrive syndrome associated with anorexia, weight loss, dehydration, and immobility. In elderly patients, failure-to-thrive may result in loss of independence and a cascade of events that increases the risk of perioperative morbidity and mortality, ultimately resulting in impaired survival. Psoas muscle mass has been used to predict morbidity and mortality after major surgical procedures in vulnerable populations with substantial comorbidities. Increasingly, psoas muscle mass is also being used to predict outcomes after RC. If patients with a high risk of impaired survival are identified preoperatively,

prehabilitative interventions can be integrated into their preparation for surgical treatment (Porserud et al., *Clin Rehab* 28(5):451-459, 2014; Friedman et al., *Nutr Clin Pract: Off Publ Am Soc Parenter Enter Nutr* 30(2):175-179, 2015). This chapter discusses the role of psoas muscle mass as a predictor of negative surgical outcomes after cystectomy.

Ahn, J., Lee, H. M., Lim, J. K., Pan, C. Q., Nguyen, M. H., Ray Kim, W., et al. (2015). Entecavir safety and effectiveness in a national cohort of treatment-naive chronic hepatitis B patients in the US - the ENUMERATE study. *Alimentary Pharmacology & Therapeutics*,

BACKGROUND: Entecavir (ETV) has been shown to be safe and efficacious in randomised controlled trials in highly selected patients with hepatitis B virus (HBV) infection. AIM: To determine the safety and effectiveness of ETV in 'real-world' HBV patients in the United States (US). METHODS: Treatment-naive HBV patients  $\geq 18$  years old who received ETV for  $\geq 12$  months between 2005 and 2013 were included in a retrospective, cohort study. Rates of ALT normalisation, undetectable HBV DNA, HBeAg and HBsAg loss/seroconversion, adverse events (AE) and clinical outcomes were evaluated. RESULTS: Of 841 patients, 658 [65% male, 83% Asian; median age 47 years] met the inclusion criteria. 36% were HBeAg+ and 9.3% cirrhotic. 89% had abnormal ALT. Baseline median HBV DNA was 5.8 log<sub>10</sub> IU/mL. Median duration of ETV treatment was 4 years. Rates of ALT normalisation at 1, 3 and 5 years were 37.2%, 48.7% and 56.2% in HBeAg+ and 39.6%, 46.8% and 55.6% in HBeAg- patients. HBV DNA was undetectable at 1, 3 and 5 years in 34.6%, 64.7% and 84.6% in HBeAg+ patients, and 81.9%, 90.3% and 96.2% in HBeAg patients. Five-year cumulative probability of HBeAg loss and seroconversion was 46% and 33.7% and HBsAg loss was 4.6%. ETV was discontinued due to adverse events in 1.2% of patients. Hepatic decompensation occurred in 0.8%, liver cancer in 2.7% and death in 0.6%. CONCLUSION: Entecavir treatment was safe in a large cohort of US patients, but ALT normalisation and hepatitis B virus DNA suppression rates were lower than previously reported in clinical trials.

Almassi, G. H., Carr, B. M., Bishawi, M., Shroyer, A. L., Quin, J. A., Hattler, B., et al. (2015). Resident versus attending surgeon graft patency and clinical outcomes in on- versus off-pump coronary artery bypass surgery. *The Journal of Thoracic and Cardiovascular Surgery*,

OBJECTIVE: Controversy exists regarding ideal approaches in teaching residents complex and/or new surgical techniques in part because consequences on patient outcomes are largely unknown. This study compared patient outcomes for cases in which residents (rather than attending surgeons) performed most of the distal anastomoses as primary surgeons, during on- and off-pump coronary artery bypass grafting (CABG). METHODS: This preapproved substudy of the Randomized On/Off Bypass (ROOBY) trial compared clinical outcomes and 1-year graft patency for cases in which residents versus attending surgeons were the primary operator. Comparisons were made between on-pump and off-pump techniques. RESULTS: From July 2003 through May 2007, a total of 1272 ROOBY nonemergent CABG patients were randomized at 16 Veterans Affairs centers where residents were active participants. Residents were the primary surgeon (ie, performed  $\geq 50\%$  of the distal anastomoses) more frequently in on-pump (77.9%) than in off-pump (67.4%) cases. Between these 2 techniques, no were found differences in baseline patient characteristics; short-term and 1-year morbidity and mortality rates were no different for residents versus attendings in CABG cases. FitzGibbon A graft patency rates were similar for resident versus attendings completed distal anastomoses for on-pump (83.0% vs 82.4%) compared with off-pump (77.2% vs 76.6%) procedures. CONCLUSIONS: In the ROOBY trial, short-term and 1-year patient outcomes and graft patency rates did not differ between resident and attending surgeons, demonstrating that with appropriate patient selection and resident supervision, residents can perform advanced, novel surgical techniques with outcomes similar to those of attending surgeons.

Amaral, A. F. S., Coton, S., Kato, B., Tan, W. C., Studnicka, M., Janson, C., et al. (2015). Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *European Respiratory Journal*, 46(4), 1104-1112.

In small studies and cases series, a history of tuberculosis has been associated with both airflow obstruction, which is characteristic of chronic obstructive pulmonary disease, and restrictive patterns on spirometry. The objective of the present study was to assess the association between a history of tuberculosis and airflow obstruction and spirometric abnormalities in adults. The study was performed in adults, aged 40 years and above, who took part in the multicentre, crosssectional, general population-based Burden of Obstructive Lung Disease study, and had

provided acceptable post-bronchodilator spirometry measurements and information on a history of tuberculosis. The associations between a history of tuberculosis and airflow obstruction and spirometric restriction were assessed within each participating centre, and estimates combined using meta-analysis. These estimates were stratified by high- and low/middle-income countries, according to gross national income. A self-reported history of tuberculosis was associated with airflow obstruction (adjusted odds ratio 2.51, 95% CI 1.83-3.42) and spirometric restriction (adjusted odds ratio 2.13, 95% CI 1.42-3.19). A history of tuberculosis was associated with both airflow obstruction and spirometric restriction, and should be considered as a potentially important cause of obstructive disease and low lung function, particularly where tuberculosis is common. Copyright © ERS 2015.

Anderson, D. E., McKenna, K. A., Glynn, J. J., Marzec, U., Hanson, S. R., & Hinds, M. T. (2014).

Thrombotic responses of endothelial outgrowth cells to protein-coated surfaces. *Cells, Tissues, Organs*, 199(4), 238-248.

There is significant clinical need for viable small-diameter vascular grafts. While there are many graft biomaterials in development, few have been clinically successful. Evaluation of grafts with a clinically relevant model is needed to drive development. This work examined extracellular matrix coatings on the thrombotic phenotype of endothelial outgrowth cells (EOCs). EOCs were tested on flat plates and tubular grafts. Flat plate studies examined collagen I, collagen IV, fibronectin and alpha-elastin coatings. EOCs attached or proliferated more readily on collagen I and fibronectin surfaces as determined by total DNA. The production of activated protein C (APC) by EOCs was also dependent on the surface coating, with collagen I and fibronectin displaying a higher activity than both collagen IV and alpha-elastin on flat plate studies. Based on these results, only collagen I and fibronectin coatings were tested on expanded polytetrafluoroethylene (ePTFE) in the ex vivo model. Tubular samples showed significantly greater tissue factor pathway inhibitor gene expression on collagen I than on fibronectin. Platelet adhesion was not significantly different, but EOCs on collagen I produced significantly lower APC than on fibronectin, suggesting that differences exist between the flat plate and tubular cultures. Overall, while the hemostatic phenotype of EOCs displayed some differences, cell responses were largely independent of the matrix coating. EOCs adhered strongly to both fibronectin- and collagen-I-coated ePTFE grafts

under ex vivo (100 ml/min) flow conditions suggesting the usefulness of this clinically relevant cell source, testing modality, and shunt model for future work examining biomaterials and cell conditioning before implantation.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, isoamyl salicylate, CAS registry number 87-20-7. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Repeated dose toxicity was determined using to have the most conservative systemic exposure derived NOAEL of 47 mg/kg/day. A dietary 13-week subchronic toxicity study conducted in rats on a suitable read across analog resulted in a MOE of 2350 while considering 10.3% absorption from skin contact and 100% from inhalation. A MOE of >100 is deemed acceptable.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, linalyl isobutyrate, CAS registry number 78-35-3. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

The use of this material under current use conditions is supported by the existing information. This material was evaluated for genotoxicity, repeated dose toxicity, developmental toxicity, reproductive toxicity, local respiratory toxicity, phototoxicity, skin sensitization potential, as well as, environmental safety. Reproductive toxicity was based on the Threshold of Toxicological Concern (TTC) of 0.03 mg/kg/day for a Cramer Class I material. The estimated systemic exposure is determined to be below this value while assuming 80% absorption from skin contact and 100% from inhalation. A systemic exposure below the TTC value is acceptable.

Aslan, J. E., David, L. L., & McCarty, O. J. T. (2015). Data detailing the platelet acetyl-lysine proteome. *Data in Brief*, 5, 368-371.

Here we detail proteomics data that describe the acetyl-lysine proteome of blood platelets (Aslan et al., 2015 [1]). An affinity purification - mass spectrometry (AP-MS) approach was used to identify proteins modified by N $\epsilon$ -lysine acetylation in quiescent, washed human platelets. The data provide insights into potential regulatory mechanisms of platelet function mediated by protein lysine acetylation. Additionally, as platelets are anucleate and lack histone proteins, they offer a unique and valuable system to study the regulation of cytosolic proteins by lysine acetylation. The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium (Vizcaino et al., 2014 [2]) via with PRIDE partner repository with the dataset identifier PXD002332. © 2015 The Authors.

Ataer-Cansizoglu, E., Taguchi, Y., Kalpathy-Cramer, J., Chiang, M. F., & Erdogmus, D. (2015).

Analysis of shape assumptions in 3D reconstruction of retina from multiple fundus images. *12th IEEE International Symposium on Biomedical Imaging, ISBI 2015, , 2015-July*. pp. 1502-1505.

Utilizing priors about the shape of retinal surface is important for accurate reconstruction. We present a detailed analysis of geometrical shape priors in the 3D reconstruction of retina. We first approximate the retinal surface either as a sphere inspired by the actual shape of the eyeball, or as a plane inspired by the 2D mosaicing approaches. Based on this approximation, we perform an initial camera localization with a 2D-to-3D registration procedure. Then, parameters of the surface and the camera poses are refined through a nonlinear least squares optimization using different shape priors. The resulting 3D model and camera poses can be used for intuitively visualizing the retinal images with a model-guided browsing interface. © 2015 IEEE.

Atwell, L. L., Zhang, Z., Mori, M., Farris, P. E., Vetto, J. T., Naik, A. M., et al. (2015). Sulforaphane bioavailability and chemopreventive activity in women scheduled for breast biopsy. *Cancer Prevention Research (Philadelphia, Pa.)*,

Epidemiological studies suggest a protective effect of cruciferous vegetables on breast cancer. Sulforaphane (SFN), an active food component derived from crucifers, has been shown to be effective in breast cancer chemoprevention. This study evaluated the chemopreventive effect of SFN on selective biomarkers from blood and breast tissues. In a 2-8-week double-blinded, randomized controlled trial, 54 women with abnormal mammograms and scheduled for breast

biopsy were randomized to consume a glucoraphanin (GFN) supplement providing SFN or placebo (n = 27). Plasma and urinary SFN metabolites, peripheral blood mononuclear cell (PBMC) histone deacetylase (HDAC) activity, and tissue biomarkers (H3K18ac, H3K9ac, HDAC3, HDAC6, Ki-67, p21) were measured before and after the intervention in benign, ductal carcinoma in situ (DCIS), or invasive ductal carcinoma (IDC) breast tissues. Within the supplement group, Ki-67 ( $p = 0.003$ ) and HDAC3 ( $p = 0.044$ ) levels significantly decreased in benign tissue. Pre-to-post-intervention changes in these biomarkers were not significantly different between treatment groups after multiple comparison adjustment. GFN supplementation was associated with a significant decrease in PBMC HDAC activity ( $p = 0.04$ ). No significant associations were observed between SFN and examined tissue biomarkers when comparing treatment groups. This study provides evidence that GFN supplementation for a few weeks is safe but may not be sufficient for producing changes in breast tissue tumor biomarkers. Future studies employing larger sample sizes should evaluate alternative dosing and duration regimens to inform dietary SFN strategies in breast cancer chemoprevention.

Babaeian, A., Babae, M., Bayestehtashk, A., & Bandarabadi, M. (2015). Nonlinear subspace clustering using curvature constrained distances. *Pattern Recognition Letters*, 68, 118-125.

The massive amount of high-dimensional data in science and engineering demands new trends in data analysis. Subspace techniques have shown remarkable success in numerous problems in computer vision and data mining, where the goal is to recover the low-dimensional structure of data in an ambient space. Traditional subspace methods like PCA and ICA assume that the data is coming from a single manifold. However, the data might come from several (possibly intersected) manifolds (surfaces). This has caused the development of new nonlinear techniques to cluster subspaces of high-dimensional data. In this paper, we propose a new algorithm for subspace clustering of data, where the data consists of several possibly intersected manifolds. To this end, we first propose a curvature constraint to find the shortest path between data points and then use it in Isomap for subspace learning. The algorithm chooses several landmark nodes at random and then checks whether there is a curvature constrained path between each landmark node and all other nodes in the neighborhood graph. It builds a binary feature vector for each point where each entry represents the connectivity of that point to a particular landmark. Then the binary

feature vectors could be used as an input of conventional clustering algorithms such as hierarchical clustering. The performed experiments on both synthetic and real data sets confirm the performance of our algorithm. © 2015 Elsevier B.V. All rights reserved.

Balikcioglu, P. G., Balikcioglu, M., Muehlbauer, M. J., Purnell, J. Q., Broadhurst, D., Freemark, M., et al. (2015). Macronutrient regulation of ghrelin and peptide YY in pediatric obesity and prader-willi syndrome. *Journal of Clinical Endocrinology and Metabolism*, 100(10), 3822-3831.

Background: The roles of macronutrients and GH in the regulation of food intake in pediatric obesity and Prader-Willi Syndrome (PWS) are poorly understood. Objective: We compared effects of high-carbohydrate (HC) and high-fat (HF) meals and GH therapy on ghrelin, insulin, peptide YY (PYY), and insulin sensitivity in children with PWS and body mass index (BMI)-matched obese controls (OCs). Methods: In a randomized, crossover study, 14 PWS (median, 11.35 y; BMI z score [BMI-z], 2.15) and 14 OCs (median, 11.97 y; BMI-z, 2.35) received isocaloric breakfast meals (HC or HF) on separate days. Blood samples were drawn at baseline and every 30 minutes for 4 hours. Mixed linear models were adjusted for age, sex, and BMI-z. Results: Relative to OCs, children with PWS had lower fasting insulin and higher fasting ghrelin and ghrelin/PYY. Ghrelin levels were higher in PWS across all postprandial time points ( $P = .0001$ ). Carbohydrate was more potent than fat in suppressing ghrelin levels in PWS ( $P < .028$ ); HC and HF were equipotent in OCs but less potent than in PWS ( $P < .011$ ). The increase in PYY following HF was attenuated in PWS ( $P < .037$ ); thus, postprandial ghrelin/PYY remained higher throughout. A lesser increase in insulin and lesser decrease in ghrelin were observed in GH-treated PWS patients than in untreated patients; PYY responses were comparable. Conclusion: Children with PWS have fasting and postprandial hyperghrelinemia and an attenuated PYY response to fat, yielding a high ghrelin/PYY ratio. GH therapy in PWS is associated with increased insulin sensitivity and lesser postprandial suppression of ghrelin. The ratio Ghrelin/PYY may be a novel marker of orexigenic drive. Copyright © 2015 by the Endocrine Society.

Bandrowski, A., Brush, M., Grethe, J. S., Haendel, M. A., Kennedy, D. N., Hill, S., et al. (2015). The resource identification initiative: A cultural shift in publishing. *F1000research*, 4

A central tenet in support of research reproducibility is the ability to uniquely identify research

resources, i.e., reagents, tools, and materials that are used to perform experiments. However, current reporting practices for research resources are insufficient to allow humans and algorithms to identify the exact resources that are reported or answer basic questions such as "What other studies used resource X" To address this issue, the Resource Identification Initiative was launched as a pilot project to improve the reporting standards for research resources in the methods sections of papers and thereby improve identifiability and reproducibility. The pilot engaged over 25 biomedical journal editors from most major publishers, as well as scientists and funding officials. Authors were asked to include Research Resource Identifiers (RRIDs) in their manuscripts prior to publication for three resource types: antibodies, model organisms, and tools (including software and databases). RRIDs represent accession numbers assigned by an authoritative database, e.g., the model organism databases, for each type of resource. To make it easier for authors to obtain RRIDs, resources were aggregated from the appropriate databases and their RRIDs made available in a central web portal ([www.scicrunch.org/resources](http://www.scicrunch.org/resources)). RRIDs meet three key criteria: they are machine readable, free to generate and access, and are consistent across publishers and journals. The pilot was launched in February of 2014 and over 300 papers have appeared that report RRIDs. The number of journals participating has expanded from the original 25 to more than 40. Here, we present an overview of the pilot project and its outcomes to date. We show that authors are generally accurate in performing the task of identifying resources and supportive of the goals of the project. We also show that identifiability of the resources pre- and post-pilot showed a dramatic improvement for all three resource types, suggesting that the project has had a significant impact on reproducibility relating to research resources. © 2015 Bandrowski A et al.

Barmack, N. H., & Yakhnitsa, V. (2015). Climbing fibers mediate vestibular modulation of both "complex" and "simple spikes" in purkinje cells. *Cerebellum (London, England)*, 14(5), 597-612. Climbing and mossy fibers comprise two distinct afferent paths to the cerebellum. Climbing fibers directly evoke a large multispiked action potential in Purkinje cells termed a "complex spike" (CS). By logical exclusion, the other class of Purkinje cell action potential, termed "simple spike" (SS), has often been attributed to activity conveyed by mossy fibers and relayed to Purkinje cells through granule cells. Here, we investigate the relative importance of climbing and mossy fiber

pathways in modulating neuronal activity by recording extracellularly from Purkinje cells, as well as from mossy fiber terminals and interneurons in folia 8-10. Sinusoidal roll-tilt vestibular stimulation vigorously modulates the discharge of climbing and mossy fiber afferents, Purkinje cells, and interneurons in folia 9-10 in anesthetized mice. Roll-tilt onto the side ipsilateral to the recording site increases the discharge of both climbing fibers (CSs) and mossy fibers. However, the discharges of SSs decrease during ipsilateral roll-tilt. Unilateral microlesions of the beta nucleus (beta-nucleus) of the inferior olive blocks vestibular modulation of both CSs and SSs in contralateral Purkinje cells. The blockage of SSs occurs even though primary and secondary vestibular mossy fibers remain intact. When mossy fiber afferents are damaged by a unilateral labyrinthectomy (UL), vestibular modulation of SSs in Purkinje cells ipsilateral to the UL remains intact. Two inhibitory interneurons, Golgi and stellate cells, could potentially contribute to climbing fiber-induced modulation of SSs. However, during sinusoidal roll-tilt, only stellate cells discharge appropriately out of phase with the discharge of SSs. Golgi cells discharge in phase with SSs. When the vestibularly modulated discharge is blocked by a microlesion of the inferior olive, the modulated discharge of CSs and SSs is also blocked. When the vestibular mossy fiber pathway is destroyed, vestibular modulation of ipsilateral CSs and SSs persists. We conclude that climbing fibers are primarily responsible for the vestibularly modulated discharge of both CSs and SSs. Modulation of the discharge of SSs is likely caused by climbing fiber-evoked stellate cell inhibition.

Bartholomew, M. L., Soules, K., Church, K., Shaha, S., Burlingame, J., Graham, G., et al. (2015).

Managing diabetes in pregnancy using cell Phone/Internet technology. *Clinical Diabetes : A Publication of the American Diabetes Association*, 33(4), 169-174.

In Brief For pregnant women with diabetes, using cell phone/Internet technology to track and report self-monitoring of blood glucose results improves compliance and satisfaction compared to using the more traditional methods of log books, telephone calls, and voicemail messages.

Beatty, H., & Svec, T. (2015). Quantifying coronal tooth discoloration caused by biodentine and EndoSequence root repair material. *Journal of Endodontics*,

INTRODUCTION: Mineral trioxide aggregate (ProRoot [PR]; Dentsply, Tulsa, OK) has been shown

to have high rates of success in various endodontic applications. A major drawback is its tendency to discolor dentin. Two new bioceramics (BD, Biodentine [BD]; Septodont, Saint Maur des Fosses, France; and EndoSequence [ES]; Brasseler, Savannah, GA) have been developed that claim to not discolor teeth. The aim of this study was to compare tooth discoloration between these 3 materials. METHODS: Forty-eight bovine mandibular incisors (4 groups, n = 12) were obtained and prepared from the apical aspect after root resection. Canals were prepared with sequentially larger ParaPost drills (Coltene/Whaledent Inc, Cuyahoga Falls, OH) to size 7 to 3 mm coronal to the cemento-enamel junction. Experimental materials were condensed into the crowns and the access sealed. Color was assessed at various times up to 2 months according to the CIE L\*a\*b\* color space system. Change in color, DeltaE, was compared among groups and over time using analysis of variance. RESULTS: For all materials, there was a sharp increase in DeltaE after placement. There was a rebound effect on day 1. After a rebound toward the initial color, all materials displayed a trend toward discoloration through the experimental period. At the end of 8 weeks, both BD and ES had discolored significantly more than either control or PR. BD and ES were not significantly different from each other. Control and PR were not significantly different from one another at the end of the experimental period. CONCLUSIONS: BD and ES discolor bovine tooth structure to a perceptible degree. At 8 weeks, this was significantly more than PR.

Bedimo, R., Kang, M., Tebas, P., Overton, E. T., Hollabaugh, K., McComsey, G. A., et al. (2015).

Effects of pegylated Interferon/Ribavirin on bone turnover markers (BTMs) in HIV/HCV co-infected patients. *AIDS Research and Human Retroviruses*,

BACKGROUND: HIV/HCV patients have a 3-fold increased fracture incidence compared to uninfected patients. The impact of HCV therapy on bone health is unclear. METHODS: We evaluated bone turnover markers (BTM) in well-controlled (HIV RNA  $\leq$  2 log HCV RNA drop at week 12) continued PEG-IFN/RBV and non-EVRs were randomized to continuation of PEG-IFN alone or observation. We assessed changes in C-terminal telopeptide of type 1 collagen (CTX; bone resorption marker) and procollagen type I Intact N-terminal propeptide (P1NP; bone formation marker), and whether BTM changes were associated with EVR, complete early virologic response (cEVR: HCV RNA < 600 IU/mL at week 12) or PEG-IFN treatment. RESULTS: 192

subjects were included. After twelve weeks of PEG-IFN/RBV, CTX and P1NP decreased: -120 pg/mL and -8.48 mug/L, respectively (both  $p < 0.0001$ ). CTX declines were greater in cEVR (N=91; vs. non-cEVR (N=101;  $p = 0.003$ ). From week 12 to 24, CTX declines were sustained among EVR patients who continued PEG-IFN/RBV ( $p = 0.027$  vs. non-EVR); and among non-EVR patients who continued PEG-IFN alone ( $p = 0.022$  vs. Observation). Median decreases of P1NP in EVR vs. non-EVR were similar at weeks 12 and 24. CONCLUSION: PEG-IFN-based therapy for chronic HCV markedly reduces bone turnover. It is unclear whether this is a direct IFN effect or a result of HCV viral clearance, or whether they will result in improved bone mineral density. Further studies with IFN-free regimens should explore these questions.

Bellur, S., Jain, M., Cuthbertson, D., Krakow, D., Shapiro, J. R., Steiner, R. D., et al. (2015). Cesarean delivery is not associated with decreased at-birth fracture rates in osteogenesis imperfecta. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*,  
PURPOSE: Osteogenesis imperfecta (OI) predisposes to recurrent fractures. Patients with the moderate to severe forms of OI present with antenatal fractures, and the mode of delivery that would be safest for the fetus is not known. METHODS: We conducted systematic analyses of the largest cohort of individuals with OI (n = 540) enrolled to date in the OI Linked Clinical Research Centers. Self-reported at-birth fracture rates were compared among individuals with OI types I, III, and IV. Multivariate analyses utilizing backward-elimination logistic regression model building were performed to assess the effect of multiple covariates, including method of delivery, on fracture-related outcomes. RESULTS: When accounting for other covariates, at-birth fracture rates did not differ based on whether delivery was by vaginal route or by cesarean delivery (CD). Increased birth weight conferred higher risk for fractures irrespective of the delivery method. In utero fracture, maternal history of OI, and breech presentation were strong predictors for choosing CD. CONCLUSION: Our study, the largest to analyze the effect of various factors on at-birth fracture rates in OI, shows that CD is not associated with decreased fracture rate. With the limitation that the fracture data were self-reported in this cohort, these results suggest that CD should be performed only for other maternal or fetal indications, not for the sole purpose of fracture prevention in OI. *Genet Med* advance online publication 01 October 2015 *Genetics in Medicine* (2015); doi:10.1038/gim.2015.131.

Benedek, G., Meza-Romero, R., Bourdette, D., & Vandenberg, A. A. (2015). The use of flow cytometry to assess a novel drug efficacy in multiple sclerosis. *Metabolic Brain Disease, 30*(4), 877-884.

Applying different technologies to monitor disease activity and treatment efficacy are essential in a complex disease such as multiple sclerosis. Combining current assays with flow cytometry could create a powerful tool for such analyses. The cell surface expression level of CD74, the MHC class II invariant chain, is a potential disease biomarker that could be monitored by FACS analysis in order to assess disease progression and the clinical efficacy of partial MHC class II constructs in treating MS. These constructs, which can bind to and down-regulate CD74 cell-surface expression on monocytes and inhibit macrophage migration inhibitory factor (MIF) effects, can reverse clinical and histological signs of EAE. These properties of partial class II constructs are highly compatible with a flow cytometry approach for monitoring CD74 expression as a possible biomarker for disease activity/ progression and as a treatment response marker. © Springer Science+Business Media New York (outside the USA) 2014.

Berry, W., & Knott, H. (2015). Ineffective counsel resulting from failure to explore history of brain injury in a capital case. *Journal of the American Academy of Psychiatry and the Law, 43*(3), 391-394.

Billings, C. J., Penman, T. M., McMillan, G. P., & Ellis, E. M. (2015). Electrophysiology and perception of speech in noise in older listeners: Effects of hearing impairment and age. *Ear and Hearing, 36*(6), 710-722.

OBJECTIVES: Speech perception in background noise is difficult for many individuals, and there is considerable performance variability across listeners. The combination of physiological and behavioral measures may help to understand sources of this variability for individuals and groups and prove useful clinically with hard-to-test populations. The purpose of this study was threefold: (1) determine the effect of signal-to-noise ratio (SNR) and signal level on cortical auditory evoked potentials (CAEPs) and sentence-level perception in older normal-hearing (ONH) and older hearing-impaired (OHI) individuals, (2) determine the effects of hearing impairment and age on CAEPs and perception, and (3) explore how well CAEPs correlate with and predict speech perception in noise. DESIGN: Two groups of older participants (15 ONH and 15 OHI) were tested

using speech-in-noise stimuli to measure CAEPs and sentence-level perception of speech. The syllable /ba/, used to evoke CAEPs, and sentences were presented in speech-spectrum background noise at four signal levels (50, 60, 70, and 80 dB SPL) and up to seven SNRs (-10, -5, 0, 5, 15, 25, and 35 dB). These data were compared between groups to reveal the hearing impairment effect and then combined with previously published data for 15 young normal-hearing individuals to determine the aging effect. RESULTS: Robust effects of SNR were found for perception and CAEPs. Small but significant effects of signal level were found for perception, primarily at poor SNRs and high signal levels, and in some limited instances for CAEPs. Significant effects of age were seen for both CAEPs and perception, while hearing impairment effects were only found with perception measures. CAEPs correlate well with perception and can predict SNR50s to within 2 dB for ONH. However, prediction error is much larger for OHI and varies widely (from 6 to 12 dB) depending on the model that was used for prediction. CONCLUSIONS: When background noise is present, SNR dominates both perception-in-noise testing and cortical electrophysiological testing, with smaller and sometimes significant contributions from signal level. A mismatch between behavioral and electrophysiological results was found (hearing impairment effects were primarily only seen for behavioral data), illustrating the possible contributions of higher order cognitive processes on behavior. It is interesting that the hearing impairment effect size was more than five times larger than the aging effect size for CAEPs and perception. Sentence-level perception can be predicted well in normal-hearing individuals; however, additional research is needed to explore improved prediction methods for older individuals with hearing impairment.

Blanke, C. D., & Curran, W. J., Jr. (2015). Progress and infrastructure for improved patient outcomes of the national cancer institute network groups. *Seminars in Oncology*, 42(5), 679-680.

Bleich, M. R., Cleary, B. L., Davis, K., Hatcher, B. J., Hewlett, P. O., & Hill, K. S. (2015). Mitigating knowledge loss a strategic imperative for nurse leaders. *Journal of Nursing Administration*, 45(10), S16-S20.

With the aging of the nursing workforce and expected retirement of large numbers of experienced nurses in the next decade, mitigating the impact that lost knowledge will have on organizational

performance and patient outcomes is critical. The authors raise awareness of the problem, summarize observations procured from hospital nurse executive regarding approaches for knowledge transfer through workforce development, and pose proactive strategies for nurse leaders who can provide direction to offset the issue before it becomes a crisis. © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Bobeck, E. N., Ingram, S. L., Hermes, S. M., Aicher, S. A., & Morgan, M. M. (2015). Ligand-biased activation of extracellular signal-regulated kinase 1/2 leads to differences in opioid induced antinociception and tolerance. *Behavioural Brain Research*,  
Opioids produce antinociception by activation of G protein signaling linked to the mu-opioid receptor (MOPr). However, opioid binding to the MOPr also activates beta-arrestin signaling. Opioids such as DAMGO and fentanyl differ in their relative efficacy for activation of these signaling cascades, but the behavioral consequences of this differential signaling are not known. The purpose of this study was to evaluate the behavioral significance of G protein and internalization dependent signaling within ventrolateral periaqueductal gray (vlPAG). Antinociception induced by microinjecting DAMGO into the vlPAG was attenuated by blocking Gα<sub>q</sub>/o protein signaling with administration of pertussis toxin (PTX), preventing internalization with administration of dynamin dominant-negative inhibitory peptide (dyn-DN) or direct inhibition of ERK1/2 with administration of the MEK inhibitor, U0126. In contrast, the antinociceptive effect of microinjecting fentanyl into the vlPAG was not altered by administration of PTX or U0126, and was enhanced by administration of dyn-DN. Microinjection of DAMGO, but not fentanyl, into the vlPAG induced phosphorylation of ERK1/2, which was blocked by inhibiting receptor internalization with administration of dyn-DN, but not by inhibition of Gα<sub>q</sub>/o proteins. ERK1/2 inhibition also prevented the development and expression of tolerance to repeated DAMGO microinjections, but had no effect on fentanyl tolerance. These data reveal that ERK1/2 activation following MOPr internalization contributes to the antinociceptive effect of some (e.g., DAMGO), but not all opioids (e.g., fentanyl) despite the known similarities for these agonists to induce beta-arrestin recruitment and internalization.

Bodhankar, S., Chen, Y., Lapato, A., Vandembark, A. A., Murphy, S. J., Saugstad, J. A., et al. (2015).

Regulatory CD8<sup>+</sup>CD122<sup>+</sup> T-cells predominate in CNS after treatment of experimental stroke in male mice with IL-10-secreting B-cells. *Metabolic Brain Disease*, 30(4), 911-924.

Clinical stroke induces inflammatory processes leading to cerebral and splenic injury and profound peripheral immunosuppression. IL-10 expression is elevated during major CNS diseases and limits inflammation in the brain. Recent evidence demonstrated that transfer of IL-10<sup>+</sup> B-cells reduced infarct volume in male C57BL/6J (wild-type, WT) recipient mice when given 24 h prior to or 4 h after middle cerebral artery occlusion (MCAO). The purpose of this study was to determine if passively transferred IL-10<sup>+</sup> B-cells can exert therapeutic and immunoregulatory effects when injected 24 h after MCAO induction in B-cell-sufficient male WT mice. The results demonstrated that IL-10<sup>+</sup> B-cell treated mice had significantly reduced infarct volumes in the ipsilateral cortex and hemisphere and improved neurological deficits vs. Vehicle-treated control mice after 60 min occlusion and 96 h of reperfusion. The MCAO-protected B-cell recipient mice had less splenic atrophy and reduced numbers of activated, inflammatory T-cells, decreased infiltration of T-cells and a less inflammatory milieu in the ischemic hemispheres compared with Vehicle-treated control mice. These immunoregulatory changes occurred in concert with the predominant appearance of IL-10-secreting CD8<sup>+</sup>CD122<sup>+</sup> Treg cells in both the spleen and the MCAO-affected brain hemisphere. This study for the first time demonstrates a major neuroprotective role for IL-10<sup>+</sup> B-cells in treating MCAO in male WT mice at a time point well beyond the ~4 h tPA treatment window, leading to the generation of a dominant IL-10<sup>+</sup>CD8<sup>+</sup>CD122<sup>+</sup> Treg population associated with spleen preservation and reduced CNS inflammation. © Springer Science+Business Media New York 2014.

Bokma, J. P., Burchill, L. J., Kovacs, A. H., Oechslin, E. N., Khairy, P., Mulder, B. J., et al. (2015).

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.

Bolon-Canedo, V., Ataer-Cansizoglu, E., Erdogmus, D., Kalpathy-Cramer, J., & Chiang, M. F. (2015). A

GMM-based feature extraction technique for the automated diagnosis of Retinopathy of

Prematurity. *12th IEEE International Symposium on Biomedical Imaging, ISBI 2015, , 2015-July.* pp. 1498-1501.

Retinopathy of Prematurity (ROP) is an ophthalmic disease that is a leading cause of childhood blindness throughout the world. Accurate diagnosis of ROP is vital to identify infants who require treatment, which can prevent blindness. Arterial tortuosity and venous dilation in the retina are important signs of ROP, so it is necessary to extract these features from points on the vessels or vessel segments. Then, an image is represented with statistics such as minimum, maximum or mean of these values. However, these statistics provide biased estimates as an image contains both healthy and abnormal vessels. In this work, we present a novel feature extraction technique that represents each image with the parameters of a two-component Gaussian Mixture Model (GMM). Using these features, we performed classification experiments on a manually segmented retinal image dataset consisting of 77 images. The results show that GMM-based features outperform other features that are based on classical statistics, with accuracy over 90%. Moreover, if the features are extracted from the whole image without distinguishing veins and arteries, proposed features provide better performance compared to using traditional statistics. © 2015 IEEE.

Bondre, I. L., Holihan, J. L., Askenasy, E. P., Greenberg, J. A., Keith, J. N., Martindale, R. G., et al.

(2015). Suture, synthetic, or biologic in contaminated ventral hernia repair. *The Journal of Surgical Research,*

BACKGROUND: Data are lacking to support the choice between suture, synthetic mesh, or biologic matrix in contaminated ventral hernia repair (VHR). We hypothesize that in contaminated VHR, suture repair is associated with the lowest rate of surgical site infection (SSI). METHODS: A multicenter database of all open VHR performed at from 2010-2011 was reviewed. All patients with follow-up of 1 mo and longer were included. The primary outcome was SSI as defined by the Centers for Disease Control and Prevention. The secondary outcome was hernia recurrence (assessed clinically or radiographically). Multivariate analysis (stepwise regression for SSI and Cox proportional hazard model for recurrence) was performed. RESULTS: A total of 761 VHR were reviewed for a median (range) follow-up of 15 (1-50) mo: there were 291(38%) suture, 303 (40%) low-density and/or mid-density synthetic mesh, and 167(22%) biologic matrix repair.

On univariate analysis, there were differences in the three groups including ethnicity, ASA, body mass index, institution, diabetes, primary versus incisional hernia, wound class, hernia size, prior VHR, fascial release, skin flaps, and acute repair. The unadjusted outcomes for SSI (15.1%; 17.8%; 21.0%;  $P = 0.280$ ) and recurrence (17.8%; 13.5%; 21.5%;  $P = 0.074$ ) were not statistically different between groups. On multivariate analysis, biologic matrix was associated with a nonsignificant reduction in both SSI and recurrences, whereas synthetic mesh associated with fewer recurrences compared to suture (hazard ratio = 0.60;  $P = 0.015$ ) and nonsignificant increase in SSI. CONCLUSIONS: Interval estimates favored biologic matrix repair in contaminated VHR; however, these results were not statistically significant. In the absence of higher level evidence, surgeons should carefully balance risk, cost, and benefits in managing contaminated ventral hernia repair.

Burrows, G. G., Van't Hof, W., Reddy, A. P., Wilmarth, P. A., David, L. L., Raber, A., et al. (2015).

Solution-phase crosstalk and regulatory interactions between multipotent adult progenitor cells and peripheral blood mononuclear cells. *Stem Cells Translational Medicine*,

: Multipotent adult progenitor cells (MAPCs) are adult adherent stromal stem cells currently being assessed in clinical trials for acute graft versus host disease with demonstrated immunomodulatory capabilities and the potential to ameliorate detrimental autoimmune and inflammation-related processes. Anti-CD3/anti-CD28 (3/28) activation of T cells within the peripheral blood mononuclear cell (PBMC) compartment was performed in the presence or absence of MAPCs. Liquid chromatography-coupled tandem mass spectrometry was used to characterize the differential secretion of proteins, and transcriptional profiling was used to monitor mRNA expression changes in both cell populations. Overall, 239 secreted and/or ectodomain-shed proteins were detected in the secretomes of PBMCs and MAPCs. In addition, 3/28 activation of PBMCs induced differential expression of 2,925 genes, and 22% of these transcripts were differentially expressed on exposure to MAPCs in Transwell. MAPCs exposed to 3/28-activated PBMCs showed differential expression of 1,247 MAPC genes. Crosstalk was demonstrated by reciprocal transcriptional regulation. Secretome proteins and transcriptional signatures were used to predict molecular activities by which MAPCs could dampen local and systemic inflammatory responses. These data support the hypothesis that MAPCs block PBMC

proliferation via cell cycle arrest coupled to metabolic stress in the form of tryptophan depletion, resulting in GCN2 kinase activation, downstream signaling, and inhibition of cyclin D1 translation. These data also provide a plausible explanation for the immune privilege reported with administration of donor MAPCs. Although most components of the major histocompatibility complex class II antigen presentation pathway were markedly transcriptionally upregulated, cell surface expression of human leukocyte antigen-DR is minimal on MAPCs exposed to 3/28-activated PBMCs. SIGNIFICANCE: This study documents experiments quantifying solution-phase crosstalk between multipotent adult progenitor cells (MAPCs) and peripheral blood mononuclear cells. The secretome and transcriptional changes quantified suggest mechanisms by which MAPCs are hypothesized to provide both local and systemic immunoregulation of inflammation. The potential impact of these studies includes development of a robust experimental framework to be used for preclinical evaluation of the specific mechanisms by which beneficial effects are obtained after treatment of patients with MAPCs.

Callon, W., Saha, S., Korthuis, P. T., Wilson, I. B., Moore, R. D., Cohn, J., et al. (2015). Which clinician questions elicit accurate disclosure of antiretroviral non-adherence when talking to patients? *AIDS and Behavior*,  
This study evaluated how clinicians assess antiretroviral (ARV) adherence in clinical encounters, and which questions elicit accurate responses. We conducted conversation analysis of audio-recorded encounters between 34 providers and 58 patients reporting ARV non-adherence in post-encounter interviews. Among 42 visits where adherence status was unknown by providers, 4 providers did not discuss ARVs (10 %), 6 discussed ARVs but did not elicit non-adherence disclosure (14 %), and 32 discussed ARVs which prompted disclosure (76 %). Questions were classified as: (1) clarification of medication ("Are you still taking the Combivir?"); (2) broad ("How's it going with your meds?"); (3) positively-framed ("Are you taking your medications regularly?"); (4) negatively-framed ("Have you missed any doses?"). Clinicians asked 75 ARV-related questions: 23 clarification, 12 broad, 17 positively-framed, and 23 negatively-framed. Negatively-framed questions were 3.8 times more likely to elicit accurate disclosure than all other question types ( $p < 0.0001$ ). Providers can improve disclosure probability by asking directly about missed doses.

Cameron, M. H., Karstens, L., Hoang, P., Bourdette, D., & Lord, S. (2015). Medications are associated with falls in people with multiple sclerosis: A prospective cohort study. *International Journal of MS Care*, 17(5), 207-214.

BACKGROUND: Medication use is associated with falls in many populations, but the relationship between medications and falls in people with multiple sclerosis (MS) is not well understood.

METHODS: The number and types of medications used by 248 ambulatory adults with MS in the United States (n = 53) and Australia (n = 195) were assessed. Participants completed fall diaries for 6 months. Associations between number and type of medications reported and falls, adjusting for age, disease severity, comorbidities, sex, and country, were evaluated using multiple logistic regression. RESULTS: Participants reported taking a median of three medications and two supplements. A total of 143 participants (58%) fell at least once in the 6 months, and 110 (44%) experienced one or more injurious falls. The adjusted relative odds of a fall or an injurious fall increased by 13% (P = .048) and 11% (P = .049), respectively, for each medication and by 43% (P = .015) and 55% (P = .001) for each neurologically active medication. Reported use of MS disease-modifying therapy was associated with 48% decreased odds of falling (P = .035) but not significantly decreased odds of injurious falls. CONCLUSIONS: Reporting use of more medications and more neurologically active medications is associated with falls and injurious falls in people with MS. Close evaluation of the need for each medication, with associated minimization of neurologically active medications in patients with MS, may help prevent falls. Use of MS disease-modifying therapies may be associated with fewer falls. This relationship needs further evaluation.

Cannell, M. B., Bouldin, E. D., Teigen, K., Akhtar, W. Z., & Andresen, E. M. (2015). The cross-sectional association between severity of non-cognitive disability and self-reported worsening memory. *Disability and Health Journal*,

BACKGROUND: Research has demonstrated a clear association between cognitive decline and non-cognitive disability; however, all of these studies focus on disability as a correlate or result of some level of cognitive impairment or dysfunction. The relationship between disability and cognition is likely a complex one, that is currently incompletely described in the literature.

OBJECTIVES: Our objective was to estimate the prevalence of long-term, non-cognitive disability

using a population-representative sample of adults aged 18 and older, and then estimate the association between long-term, non-cognitive disability and self-reported worsening memory. METHODS: Using the 2009 Florida Behavioral Risk Factor Surveillance System (BRFSS), we measured the relationship between non-cognitive disability and worsening memory using multivariable logistic regression analysis weighted to account for the complex sampling design of the BRFSS. We also estimated the adjusted odds of worsening memory by disability severity, classified according to the types of assistance needed. RESULTS: Approximately 18% (95% confidence interval = (16%, 19%)) of Floridians were living with a long-term, non-cognitive disability in 2009. Among adults with no disability during or prior to the last year, only 5% reported worsening memory. The proportion of Floridians reporting worsening memory increases with increasing severity of disability-related limitations. In a multivariable logistic regression model, odds of worsening memory increased significantly with severity of disability-related limitations. CONCLUSIONS: These results highlight the association between non-cognitive disability and subsequent increased odds of worsening memory, independent of several other known risk factors, and a dose-response association with disability-related limitations.

Capp, R., Sun, B., Boatright, D., & Gross, C. (2015). The impact of emergency department observation units on united states emergency department admission rates. *Journal of Hospital Medicine, 10*(11), 738-742.

OBJECTIVE: Prior studies suggesting that the presence of emergency department (ED) observation units decrease overall ED hospital admissions have been either single-center studies or based on model simulations. The objective of this preliminary national study is to determine if the presence of ED observation units is associated with hospitals having lower ED admission rates. METHODS: We conducted a retrospective cross-sectional analysis using the 2010 National Hospital Ambulatory Care Survey and estimated ED risk-standardized hospital admission rates (RSHAR) for each center. The following were excluded from the study: ages <18 years, leaving prior to completion of ED visit, died in the ED, transferred to another facility, and missing disposition. Hospitals with less than 30 ED visits or unknown observation unit status were also excluded. We used linear regression analysis to determine the association between ED RSHAR and presence of observation units. RESULTS: There were 24,232 ED visits in 315 hospitals in the

United States. Of these, 82 (20.6%) hospitals had an ED observation unit. The average ED risk-standardized hospital admission rates for hospitals with observation units and without hospital observation units were 13.7% (95% confidence interval [CI]: 11.3-16.0) and 16.0% (95% CI: 14.1-17.7), respectively. The difference of 2.3% was not statistically significant. CONCLUSIONS: In this preliminary study, we did not find an association between the presence of observation units and ED hospital admission rates. Further studies with larger sample sizes should be performed to further evaluate the impact of ED observation units on ED hospital admission rates. *Journal of Hospital Medicine* 2015;10:738-742. (c) 2015 Society of Hospital Medicine.

Caughey, A. B., Puljic, A., & Page, J. (2015). Reply. *American Journal of Obstetrics and Gynecology*, 213(4), 594-595.

Cawthon, P. M., Blackwell, T. L., Cauley, J., Kado, D. M., Barrett-Connor, E., Lee, C. G., et al. (2015). Evaluation of the usefulness of consensus definitions of sarcopenia in older men: Results from the observational osteoporotic fractures in men cohort study. *Journal of the American Geriatrics Society*,

OBJECTIVE: To evaluate the associations between definitions of sarcopenia and clinical outcomes and the ability of the definitions to discriminate those with a high likelihood of having these outcomes from those with a low likelihood. DESIGN: Osteoporotic Fractures in Men Study.

SETTING: Six clinical centers. PARTICIPANTS: Community-dwelling men aged 65 and older (N = 5,934). MEASUREMENTS: Sarcopenia definitions from the International Working Group, European Working Group on Sarcopenia in Older Persons, Foundation for the National Institutes of Health Sarcopenia Project, Baumgartner, and Newman were evaluated. Recurrent falls were defined as two or more self-reported falls in the year after baseline (n = 694, 11.9%). Incident hip fractures (n = 207, 3.5%) and deaths (n = 2,003, 34.1%) were confirmed according to central review of medical records over 9.8 years. Self-reported functional limitations were assessed at baseline and 4.6 years later. Logistic regression or proportional hazards models were used to estimate associations between sarcopenia and falls, hip fractures, and death. The discriminative ability of the sarcopenia definitions (vs reference models) for these outcomes was evaluated using area under the receiver operating characteristic curve or C-statistics. Referent models included age

alone for falls, functional limitations and mortality, and age and bone mineral density for hip fractures. RESULTS: The association between sarcopenia according to the various definitions and risk of falls, functional limitations, and hip fractures was variable; all definitions were associated with greater risk of death, but none of the definitions materially changed discrimination based on the AUC and C-statistic when compared with reference models (change  $\leq 1\%$  in all models). CONCLUSION: Sarcopenia definitions as currently constructed did not consistently improve prediction of clinical outcomes in relatively healthy older men.

Chang, H., Spellman, P. T., & Parvin, B. (2015). Predictive sparse morphometric context for classification of histology sections. *12th IEEE International Symposium on Biomedical Imaging, ISBI 2015, , 2015-July*. pp. 1004-1007.

Classification of histology sections from large cohorts, in terms of distinct regions of microanatomy (e.g., tumor, stroma, normal), enables the quantification of tumor composition, and the construction of predictive models of the clinical outcome. To tackle the batch effects and biological heterogeneities that are persistent in large cohorts, sparse cellular morphometric context has recently been developed for invariant representation of the underlying properties in the data, which summarizes cellular morphometric features at various locations and scales, and leads to a system with superior performance for classification of microanatomy and histopathology. However, the sparse optimization protocol for the calculation of sparse cellular morphometric features is not scalable for large scale classification. To improve the scalability of systems, based on sparse morphometric context, we propose the predictive sparse morphometric context in place of the original implementation, which approximates the sparse cellular morphometric feature through a non-linear regressor that is jointly learned with an over-complete dictionary in an unsupervised manner. Experimental results indicates over 50 times speedup compared to our previous implementation with the help of non-linear regressor; while producing competitive performance. © 2015 IEEE.

Charlesworth, C. J., Smit, E., Lee, D. S., Alramadhan, F., & Odden, M. C. (2015). Polypharmacy among adults aged 65 years and older in the united states: 1988-2010. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 70(8)*, 989-995.

**BACKGROUND:** Older adults frequently have several chronic health conditions which require multiple medications. We illustrated trends in prescription medication use over 20 years in the United States, and described characteristics of older adults using multiple medications in 2009-2010. **METHODS:** Participants included 13,869 adults aged 65 years and older in the National Health & Nutrition Examination Survey (1988-2010). Prescription medication use was verified by medication containers. Potentially inappropriate medications were defined by the 2003 Beers Criteria. **RESULTS:** Between 1988 and 2010 the median number of prescription medications used among adults aged 65 and older doubled from 2 to 4, and the proportion taking  $\geq 5$  medications tripled from 12.8% (95% confidence interval: 11.1, 14.8) to 39.0% (35.8, 42.3). These increases were driven, in part, by rising use of cardioprotective and antidepressant medications. Use of potentially inappropriate medications decreased from 28.2% (25.5, 31.0) to 15.1% (13.2, 17.3) between 1988 and 2010. Higher medication use was associated with higher prevalence of functional limitation, activities of daily living limitation, and confusion/memory problems in 2009-2010, although these associations did not remain after adjustment for covariates. In multivariable models, older age, number of chronic conditions, and annual health care visits were associated with increased odds of using both 1-4 and  $\geq 5$  medications. Additionally, body mass index, higher income-poverty ratio, former smoking, and non-black non-white race were associated with use of  $\geq 5$  medications. **CONCLUSIONS:** Prescription medication use increased dramatically among older adults between 1988 and 2010. Contemporary older adults on multiple medications have worse health status compared with those on less medications, and appear to be a vulnerable population.

Chatzi, C., Schnell, E., & Westbrook, G. L. (2015). Localized hypoxia within the SGZ determines the early survival of newborn hippocampal granule cells. *Elife*, 4, 10.7554/eLife.08722.

The majority of adult hippocampal newborn cells die during early differentiation from intermediate progenitors (IPCs) to immature neurons. Neural stem cells in vivo are located in a relative hypoxic environment, and hypoxia enhances their survival, proliferation and stemness in vitro. Thus, we hypothesized that migration of IPCs away from hypoxic zones within the SGZ might result in oxidative damage, thus triggering cell death. Hypoxic niches were observed along the SGZ, composed of adult NSCs and early IPCs, and oxidative byproducts were present in

adjacent late IPCs and neuroblasts. Stabilizing hypoxia inducible factor-1alpha with dimethyloxallyl glycine increased early survival, but not proliferation or differentiation, in neurospheres in vitro and in newly born SGZ cells in vivo. Rescue experiments in Baxfl/fl mutants supported these results. We propose that localized hypoxia within the SGZ contributes to the neurogenic microenvironment and determines the early, activity-independent survival of adult hippocampal newborn cells.

Chen, M., Peters, A., Huang, T., & Nan, X. (2015). Ras dimer formation as a new signaling mechanism and potential cancer therapeutic target. *Mini Reviews in Medicinal Chemistry*, 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.

Chiovaro, J. (2015). Capsule commentary on turner et al., chronic opioid therapy urine drug testing in primary care: Prevalence and predictors of aberrant results. *Journal of General Internal Medicine*, 30(2), 241-014-3091-7.

Colley, P., Mace, J. C., Schaberg, M. R., Smith, T. L., & Tabae, A. (2015). Impact of educational intervention on the interrater agreement of nasal endoscopy interpretation. *Laryngoscope*, 125(10), 2259-2265.

Objective Nasal endoscopy is integral to the evaluation of sinonasal disorders. However, prior studies have shown significant variability in the interrater agreement of nasal endoscopy interpretation among practicing rhinologists. The objective of the current study is to evaluate the interrater agreement of nasal endoscopy among otolaryngology residents from a single training program at baseline and following an educational intervention. Methods Eleven otolaryngology

residents completed nasal endoscopy grading forms for eight digitally recorded nasal endoscopic examinations. An instructional lecture reviewing nasal endoscopy interpretation was subsequently provided. The residents then completed grading forms for eight different nasal endoscopic examinations. Interrater agreement among residents for the pre- and postlecture videos was calculated using the unweighted Fleiss' kappa (Kf) statistic and intraclass correlation agreement (ICC). Results Interrater agreement improved from a baseline level of fair (Kf range 0.268-0.383) to a posteducational level of moderate (Kf range 0.401-0.547) for nasal endoscopy findings of middle meatus mucosa, middle turbinate mucosa, middle meatus discharge, sphenoethmoid recess mucosa, sphenoethmoid recess discharge, and atypical lesions (ICC,  $P < 0.001$ ). The baseline level of agreement for evaluation of nasal septum deviation was poor/fair and did not improve following educational intervention. Conclusions This study demonstrates a limited baseline level of interrater agreement of nasal endoscopy interpretation among otolaryngology residents. The interrater agreement for the majority of the characteristics that were evaluated improved after educational intervention. Further study is needed to improve nasal endoscopy interpretation. © 2015 The American Laryngological, Rhinological and Otological Society, Inc.

Connelly, C. R., Laird, A., Barton, J. S., Fischer, P. E., Krishnaswami, S., Schreiber, M. A., et al.

(2015). A clinical tool for the prediction of venous thromboembolism in pediatric trauma patients. *JAMA Surgery*, , 1-8.

Importance: Although rare, the incidence of venous thromboembolism (VTE) in pediatric trauma patients is increasing, and the consequences of VTE in children are significant. Studies have demonstrated increasing VTE risk in older pediatric trauma patients and improved VTE rates with institutional interventions. While national evidence-based guidelines for VTE screening and prevention are in place for adults, none exist for pediatric patients, to our knowledge. Objectives: To develop a risk prediction calculator for VTE in children admitted to the hospital after traumatic injury to assist efforts in developing screening and prophylaxis guidelines for this population.

Design, Setting, and Participants: Retrospective review of 536423 pediatric patients 0 to 17 years old using the National Trauma Data Bank from January 1, 2007, to December 31, 2012. Five mixed-effects logistic regression models of varying complexity were fit on a training data set. Model validity was determined by comparison of the area under the receiver operating

characteristic curve (AUROC) for the training and validation data sets from the original model fit. A clinical tool to predict the risk of VTE based on individual patient clinical characteristics was developed from the optimal model. Main Outcome and Measure: Diagnosis of VTE during hospital admission. Results: Venous thromboembolism was diagnosed in 1141 of 536423 children (overall rate, 0.2%). The AUROCs in the training data set were high (range, 0.873-0.946) for each model, with minimal AUROC attenuation in the validation data set. A prediction tool was developed from a model that achieved a balance of high performance (AUROCs, 0.945 and 0.932 in the training and validation data sets, respectively;  $P = .048$ ) and parsimony. Points are assigned to each variable considered (Glasgow Coma Scale score, age, sex, intensive care unit admission, intubation, transfusion of blood products, central venous catheter placement, presence of pelvic or lower extremity fractures, and major surgery), and the points total is converted to a VTE risk score. The predicted risk of VTE ranged from 0.0% to 14.4%. Conclusions and Relevance: We developed a simple clinical tool to predict the risk of developing VTE in pediatric trauma patients. It is based on a model created using a large national database and was internally validated. The clinical tool requires external validation but provides an initial step toward the development of the specific VTE protocols for pediatric trauma patients.

Connelly, C. R., & Schreiber, M. A. (2015). Endpoints in resuscitation. *Current Opinion in Critical Care*, 21(6), 512-519.

PURPOSE OF REVIEW: Shock occurs because of a failure to deliver adequate oxygen to meet the metabolic demands of the body resulting in metabolic acidosis, inflammation, and coagulopathy. Resuscitation is the process of treating shock in an attempt to restore normal physiology. Various hemodynamic, metabolic, and regional endpoints have been described to evaluate the degree of shock and guide resuscitation efforts. We will briefly describe these endpoints, and propose damage control resuscitation as an additional endpoint. RECENT FINDINGS: Serum lactate, base deficit, and pH are well established endpoints of resuscitation that provide valuable information when trended over time; however, a single value is inadequate to determine adequacy of resuscitation. Rapid normalization of central venous oxygen concentration has been associated with improved survival, and bedside transthoracic echocardiography can be a reliable assessment of volume status. In hypovolemic/hemorrhagic shock, early hypotensive, or controlled

resuscitation strategies have been associated with improved survival, and hemostatic strategies guided by thrombelastography using a balanced transfusion approach result in improved hemostasis. SUMMARY: Numerous endpoints are available; however, no single endpoint is universally applicable. Damage control resuscitation strategies have demonstrated improved survival, hemostasis, and less early death from exsanguination, suggesting that hemorrhage control should be an additional endpoint in resuscitation.

Cook, M. R., Graff-Baker, A. N., Moren, A. M., Brown, S., Fair, K. A., Kiraly, L. N., et al. (2015). A disease-specific hybrid rotation increases opportunities for deliberate practice. *Journal of Surgical Education*,

IMPORTANCE: Incorporating deliberate practice (DP) into residency curricula may optimize education. DP includes educationally protected time, continuous expert feedback, and a focus on a limited number of technical skills. It is strongly associated with mastery level learning.

OBJECTIVE: Determine if a multidisciplinary breast rotation (MDB) increases DP opportunities.

DESIGN: Beginning in 2010, interns completed the 4-week MDB. Three days a week were spent in surgery and surgical clinic. Half-days were in breast radiology, pathology, medical oncology, and didactics. The MDB was retrospectively compared with a traditional community rotation (TCR) and a university surgical oncology service (USOS) using rotation feedback and resident operative volume. Data are presented as mean +/- standard deviation. SETTING: Oregon Health and Science University in Portland, Oregon; an academic tertiary care general surgery residency program. PARTICIPANTS: General surgery residents at Oregon Health and Science University participating in either the MDB, TCR or USOS. RESULTS: A total of 31 interns rated the opportunity to perform procedures significantly higher for MDB than TCR or USOS (4.6 +/- 0.6 vs 4.2 +/- 0.9 and 4.1 +/- 1.0,  $p < 0.05$ ). MDB was rated higher than TCR on quality of faculty teaching and educational materials (4.5 +/- 0.7 vs 4.1 +/- 0.9 and 4.0 +/- 1.2 vs 3.5 +/- 1.0,  $p < 0.05$ ). Interns operated more on the MDB than on the USOS and were more focused on breast resections, lymph node dissections, and port placements than on the traditional surgical rotation or USOS. CONCLUSIONS: The MDB incorporates multidisciplinary care into a unique, disease-specific, and educationally focused rotation. It is highly rated and affords a greater opportunity

for DP than either the USOS or TCR. DP is strongly associated with mastery learning and this novel rotation structure could maximize intern education in the era of limited work hours.

Coronado, G. D., Retecki, S., Schneider, J., Taplin, S. H., Burdick, T., & Green, B. B. (2015).

Recruiting community health centers into pragmatic research: Findings from STOP CRC. *Clinical Trials (London, England)*,

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.

Crawford, J. D., Landry, G. J., Moneta, G. L., & Mitchell, E. L. (2015). Outcomes of unilateral graft limb excision for infected aortobifemoral graft limb. *Journal of Vascular Surgery*,

OBJECTIVE: Aortobifemoral graft (ABFG) infections presenting with apparent single-limb involvement can be managed with unilateral graft limb excision or complete graft removal. This study aimed to identify outcomes of unilateral graft limb excision for infected ABFGs and factors predictive of subsequent contralateral or main body graft limb infection. METHODS: A retrospective review of patients treated with unilateral graft limb excision for infection of an isolated limb of an ABFG from 2001 to July 2014 was performed. Endovascular and aortic tube graft infections were excluded. Outcomes were freedom from contralateral graft limb excision, overall survival, and factors predicting subsequent contralateral limb or main body infection. RESULTS: Fifteen patients underwent unilateral graft limb excision and revascularization for treatment of an infected ABFG isolated to one graft limb. Indications for the original ABFG were aortoiliac occlusive disease in 11 patients and aortoiliac aneurysm in 4 patients. All patients presented with clinical evidence consistent with unilateral graft limb infection and clinical findings confirmed radiographically. Unilateral graft explantation was performed for isolated infrainguinal graft limb infection with no retroperitoneal infection on exploration or if patients were too ill to tolerate total graft explantation despite infection in the retroperitoneum. Seven patients, all of whom underwent initial operation for aortoiliac occlusive disease, developed contralateral limb infection at a median follow-up of 23.2 months after unilateral excision. The remaining eight patients remained free of contralateral graft limb infection at median follow-up of 38.8 months. Patient demographics were similar between the two groups. Factors predictive of contralateral graft limb infection included an ABFG placed for aortoiliac occlusive disease ( $P = .03$ ) and culture evidence of infection above the inguinal ligament ( $P = .07$ ; positive predictive value of 71%). Median duration of targeted antibiotic therapy was 42 days, and neither duration of antibiotics nor cultured microorganism predicted recurrent graft infection. Overall mortality was 40% and was similar between patients who developed contralateral or main body graft infection and those who did not. There was no limb loss, and overall median follow-up was 44.7 months.

CONCLUSIONS: Isolated unilateral infection of an ABFG limb can be managed with single graft limb excision, provided the infection is isolated to the infrainguinal graft segment. Factors predicting subsequent contralateral or main body graft infection include ABFGs originally placed for aortoiliac occlusive disease and culture-positive graft infection above the inguinal ligament.

Curtis, J. A., Tanner, P., Hull, C. M., & Leachman, S. A. (2015). Reply to: "nail curing UV lamps: Trivial exposure not cause for public alarm". *Journal of the American Academy of Dermatology*, 73(5), e187.

de Vries, Y. A., Turner, E. H., & Roest, A. M. (2015). Retraction of biased journal articles. *BMJ (Clinical Research Ed.)*, 351, h5497.

Denneson, L. M., Williams, H. B., Kaplan, M. S., McFarland, B. H., & Dobscha, S. K. (2015). Treatment of veterans with mental health symptoms in VA primary care prior to suicide. *General Hospital Psychiatry*,

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

Desai, S. R., Frieden, I. J., Gelfand, J. M., High, W., Kavanaugh, A., Marghoob, A. A., et al. (2015).

Updates on psoriasis and cutaneous oncology: Proceedings from the 2015 MauiDerm meeting.

*The Journal of Clinical and Aesthetic Dermatology*, 8(9 Suppl), S4-S26.

Dewland, T. A., Vittinghoff, E., Harris, T. B., Magnani, J. W., Liu, Y., Hsu, F. C., et al. (2015).

Inflammation as a mediator of the association between race and atrial fibrillation: Results from the health, aging, and body composition study. *JACC.Clinical Electrophysiology*, 1(4), 248-255.

BACKGROUND: Despite a lower prevalence of established atrial fibrillation (AF) risk factors,

Whites exhibit substantially higher rates of this arrhythmia compared to Blacks. The mechanism underlying this observation is not known. Both inflammation and obesity are risk factors for AF,

and adipose tissue is a known contributor to systemic inflammation. OBJECTIVES: We sought to determine the degree to which racial differences in AF risk are explained by differences in

inflammation and adiposity. METHODS: Baseline serum inflammatory biomarker concentrations and abdominal adiposity (assessed by computed tomography) were quantified in a subset of

Black and White participants without prevalent AF in the Health, Aging, and Body Composition (Health ABC) Study. Participants were prospectively followed for the diagnosis of AF using study

ECGs and Medicare claims data. Cox proportional hazards models were used to determine the adjusted relative hazard of incident AF between races before and after biomarker adjustment.

RESULTS: Among 2,768 participants (43% Black), 721 developed incident AF over a median follow up of 10.9 years. White race was associated with a heightened adjusted risk of incident AF

(HR 1.55, 95% CI 1.30 to 1.84,  $p < 0.001$ ). Abdominal adiposity was not associated with AF

when added to the adjusted model. Among the studied biomarkers, adiponectin, TNF-alpha, TNF-alpha SR I, and TNF-alpha SR II concentrations were each higher among Whites and

independently associated with a greater risk of incident AF. Together, these inflammatory

cytokines mediated 42% (95% CI 15 to 119%,  $p = 0.004$ ) of the adjusted race-AF association.

CONCLUSIONS: Systemic inflammatory pathways significantly mediate the heightened risk of AF among Whites. The higher level of systemic inflammation and concomitant increased AF risk in

Whites is not explained by racial differences in abdominal adiposity or the presence of other pro-inflammatory cardiovascular comorbidities.

Deyo, R. A. (2015). Can parsimonious practice please patients and practitioners? the case of spine imaging. *Journal of General Internal Medicine*,

Deyo, R. A., Dworkin, S. F., Amtmann, D., Andersson, G., Borenstein, D., Carragee, E., et al. (2014). Report of the NIH task force on research standards for chronic low back pain. *The Spine Journal : Official Journal of the North American Spine Society*, 14(8), 1375-1391.

Despite rapidly increasing intervention, functional disability due to chronic low back pain (cLBP) has increased in recent decades. We often cannot identify mechanisms to explain the major negative impact cLBP has on patients' lives. Such cLBP is often termed non-specific and may be due to multiple biologic and behavioral etiologies. Researchers use varied inclusion criteria, definitions, baseline assessments, and outcome measures, which impede comparisons and consensus. Therefore, NIH Pain Consortium charged a Research Task Force (RTF) to draft standards for research on cLBP. The resulting multidisciplinary panel recommended using 2 questions to define cLBP; classifying cLBP by its impact (defined by pain intensity, pain interference, and physical function); use of a minimum dataset to describe research participants (drawing heavily on the PROMIS methodology); reporting "responder analyses" in addition to mean outcome scores; and suggestions for future research and dissemination. The Pain Consortium has approved the recommendations, which investigators should incorporate into NIH grant proposals. The RTF believes that these recommendations will advance the field, help to resolve controversies, and facilitate future research addressing the genomic, neurologic, and other mechanistic substrates of chronic low back pain. We expect that the RTF recommendations will become a dynamic document and undergo continual improvement. PERSPECTIVE: A task force was convened by the NIH Pain Consortium with the goal of developing research standards for chronic low back pain. The results included recommendations for definitions, a minimum dataset, reporting outcomes, and future research. Greater consistency in reporting should facilitate comparisons among studies and the development of phenotypes.

Dille, M. F., McMillan, G. P., Helt, W. J., Konrad-Martin, D., & Jacobs, P. (2015). A store-and-forward tele-audiology solution to promote efficient screenings for ototoxicity during cisplatin cancer treatment. *Journal of the American Academy of Audiology*, 26(9), 750-760.

**BACKGROUND:** Tele-audiology improves access, controls cost, and improves efficiency of many aspects within health care. We have developed and validated a device, the ototoxicity identification device (OtoID), which enables remote hearing monitoring by a patient during chemotherapy treatment. Aspects of the design such as patient self-testing and texting of results to the audiology clinic are important features of this device. **PURPOSE:** The purpose of this article is to present the efficacy and effectiveness of the OtoID hearing screener. **RESEARCH DESIGN:** A repeated measures design was used in this study. **STUDY SAMPLE:** Twenty-one veterans undergoing cisplatin chemotherapy were recruited in this study. **DATA COLLECTION AND ANALYSIS:** Participants were tested using the OtoID at each cisplatin treatment by an audiologist using the manual mode of test and the participant using the automated mode of test. Test sensitivity and specificity were developed from the detection (yes/no) of an American Speech-Language-Hearing Association (ASHA) change in hearing. **RESULTS:** The OtoID had a test sensitivity of 80.6% and specificity of 85.3%. A logistic regression model analysis of the probability of an ASHA shift identified by the automated OtoID was conducted. Separate models were fit to establish effects of age, average baseline thresholds in the sensitive range for ototoxicity (SRO), and dose of cisplatin on the probability of a positive hearing change result. Interactions were also included to evaluate these effects on the sensitivity and false-positive rates of the automated test. Results indicated no statistically significant effects of age, of baseline hearing in the SRO frequencies, or of cisplatin dose. **CONCLUSIONS:** The OtoID automated test can be recommended for use. The automated test provides significant personnel efficiencies. The modem with simple text messaging function recently added to the device improves on these efficiencies.

Driessen, E., Hollon, S. D., Bockting, C. L., Cuijpers, P., & Turner, E. H. (2015). Does publication bias inflate the apparent efficacy of psychological treatment for major depressive disorder? A systematic review and meta-analysis of US national institutes of health-funded trials. *PLoS One*, *10*(9), e0137864.

**BACKGROUND:** The efficacy of antidepressant medication has been shown empirically to be overestimated due to publication bias, but this has only been inferred statistically with regard to psychological treatment for depression. We assessed directly the extent of study publication bias

in trials examining the efficacy of psychological treatment for depression. METHODS AND FINDINGS: We identified US National Institutes of Health grants awarded to fund randomized clinical trials comparing psychological treatment to control conditions or other treatments in patients diagnosed with major depressive disorder for the period 1972-2008, and we determined whether those grants led to publications. For studies that were not published, data were requested from investigators and included in the meta-analyses. Thirteen (23.6%) of the 55 funded grants that began trials did not result in publications, and two others never started. Among comparisons to control conditions, adding unpublished studies (Hedges'  $g = 0.20$ ; CI95%  $-0.11 \sim 0.51$ ;  $k = 6$ ) to published studies ( $g = 0.52$ ;  $0.37 \sim 0.68$ ;  $k = 20$ ) reduced the psychotherapy effect size point estimate ( $g = 0.39$ ;  $0.08 \sim 0.70$ ) by 25%. Moreover, these findings may overestimate the "true" effect of psychological treatment for depression as outcome reporting bias could not be examined quantitatively. CONCLUSION: The efficacy of psychological interventions for depression has been overestimated in the published literature, just as it has been for pharmacotherapy. Both are efficacious but not to the extent that the published literature would suggest. Funding agencies and journals should archive both original protocols and raw data from treatment trials to allow the detection and correction of outcome reporting bias. Clinicians, guidelines developers, and decision makers should be aware that the published literature overestimates the effects of the predominant treatments for depression.

Dufour, B. D., & McBride, J. L. (2016). Intravascular AAV9 administration for delivering RNA silencing constructs to the CNS and periphery. *Methods in Molecular Biology (Clifton, N.J.)*, 1364, 261-275. Viral vector delivery of RNA silencing constructs, when administered into vasculature, typically results in poor central nervous system (CNS) transduction due to the inability of the vector to cross the blood-brain barrier (BBB). However, adeno-associated virus serotype 9 (AAV9) has the ability to cross the BBB and robustly transduce brain parenchyma and peripheral tissues at biologically meaningful levels when injected intravenously. Recent work by our lab has shown that this method can be used to deliver RNA silencing constructs, resulting in significant reductions in gene expression in multiple brain regions and in peripheral tissues. Here, we outline a method for delivery of AAV9 vectors expressing RNA interference (RNAi) constructs that lead to robust simultaneous transduction of mouse peripheral tissues and the CNS following a single

injection into the jugular vein. Additionally, we outline methods for necropsy and immunofluorescence to detect AAV9 transduction patterns in the rodent CNS following a vascular delivery.

Ellison, D. H., Terker, A. S., & Gamba, G. (2015). Potassium and its discontents: New insight, new treatments. *Journal of the American Society of Nephrology : JASN*,

Hyperkalemia is common in patients with impaired kidney function or who take drugs that inhibit the renin-angiotensin-aldosterone axis. During the past decade, substantial advances in understanding how the body controls potassium excretion have been made, which may lead to improved standard of care for these patients. Renal potassium disposition is primarily handled by a short segment of the nephron, comprising part of the distal convoluted tubule and the connecting tubule, and regulation results from the interplay between aldosterone and plasma potassium. When dietary potassium intake and plasma potassium are low, the electroneutral sodium chloride cotransporter is activated, leading to salt retention. This effect limits sodium delivery to potassium secretory segments, limiting potassium losses. In contrast, when dietary potassium intake is high, aldosterone is stimulated. Simultaneously, potassium inhibits the sodium chloride cotransporter. Because more sodium is then delivered to potassium secretory segments, primed by aldosterone, kaliuresis results. When these processes are disrupted, hyperkalemia results. Recently, new agents capable of removing potassium from the body and treating hyperkalemia have been tested in clinical trials. This development suggests that more effective and safer approaches to the prevention and treatment of hyperkalemia may be on the horizon.

Erickson, T., & Nicolson, T. (2015). Identification of sensory hair-cell transcripts by thiouracil-tagging in zebrafish. *BMC Genomics*, 16(1), 842-015-2072-5.

BACKGROUND: Sensory hair cells are exquisitely sensitive to mechanical stimuli and as such, are prone to damage and apoptosis during dissections or in vitro manipulations. Thiouracil (TU)-tagging is a noninvasive method to label cell type-specific transcripts in an intact organism, thereby meeting the challenge of how to analyze gene expression in hair cells without the need to sort cells. We adapted TU-tagging to zebrafish to identify novel transcripts expressed in the

sensory hair cells of the developing acoustico-lateralis organs. **METHODS:** We created a transgenic line of zebrafish expressing the *T.gondii* uracil phospho-ribosyltransferase (UPRT) enzyme specifically in the hair cells of the inner ear and lateral line organ. RNA was labeled by exposing 3 days post-fertilization (dpf) UPRT transgenic larvae to 2.5 mM 4-thiouracil (4TU) for 15 hours. Following total RNA isolation, poly(A) mRNA enrichment, and purification of TU-tagged RNA, deep sequencing was performed on the input and TU-tagged RNA samples. **RESULTS:** Analysis of the RNA sequencing data revealed the expression of 28 transcripts that were significantly enriched (adjusted p-value < 0.05) in the UPRT TU-tagged RNA relative to the input sample. Of the 25 TU-tagged transcripts with mammalian homologs, the expression of 18 had not been previously demonstrated in zebrafish hair cells. The hair cell-restricted expression for 17 of these transcripts was confirmed by whole mount mRNA in situ hybridization in 3 dpf larvae. **CONCLUSIONS:** The hair cell-restricted pattern of expression of these genes offers insight into the biology of this receptor cell type and may serve as useful markers to study the development and function of sensory hair cells. In addition, our study demonstrates the utility of TU-tagging to study nascent transcripts in specific cell types that are relatively rare in the context of the whole zebrafish larvae.

Fazio, S. (2015). The role of PCSK9 in intestinal lipoprotein metabolism: Synergism of statin and ezetimibe. *Atherosclerosis.Supplements*, 17, 23-26.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a major role in the regulation of lipoprotein metabolism, mostly through control of low-density lipoprotein receptor degradation. Depletion of cellular cholesterol causes a compensatory increase in plasma PCSK9 levels, which can diminish the cholesterol-lowering power of statins and may lead to the overproduction of intestinal lipoproteins, mainly thorough the up regulation of microsomal triglyceride transfer protein and the Niemann-Pick C1-like 1 protein, the target of ezetimibe. Thus, ezetimibe therapy may counter this unwanted effect of statins, providing an additional theoretical rationale for combining the effect of ezetimibe on intestinal cholesterol absorption and that of statins on cholesterol synthesis.

Feng, Z., Puri, S., Moudgil, T., Wood, W., Hoyt, C. C., Wang, C., et al. (2015). Multispectral imaging of formalin-fixed tissue predicts ability to generate tumor-infiltrating lymphocytes from melanoma. *Journal for Immunotherapy of Cancer*, 3, 47-015-0091-z. eCollection 2015.

**BACKGROUND:** Adoptive T cell therapy (ACT) has shown great promise in melanoma, with over 50 % response rate in patients where autologous tumor-reactive tumor-infiltrating lymphocytes (TIL) can be cultured and expanded. A major limitation of ACT is the inability to generate or expand autologous tumor-reactive TIL in 25-45 % of patients tested. Methods that successfully identify tumors that are not suitable for TIL generation by standard methods would eliminate the costs of fruitless expansion and enable these patients to receive alternate therapy immediately.

**METHODS:** Multispectral fluorescent immunohistochemistry with a panel including CD3, CD8, FoxP3, CD163, PD-L1 was used to analyze the tumor microenvironment in 17 patients with melanoma among our 36-patient cohort to predict successful TIL generation. Additionally, we compared tumor fragments and enzymatic digestion of tumor samples for efficiency in generating tumor-reactive TIL. **RESULTS:** Tumor-reactive TIL were generated from 21/36 (58 %) of melanomas and for 12/13 (92 %) tumors where both enzymatic and fragment methods were compared. TIL generation was successful in 10/13 enzymatic preparations and in 10/13 fragment cultures; combination of both methods resulted in successful generation of autologous tumor-reactive TIL in 12/13 patients. In 17 patients for whom tissue blocks were available, IHC analysis identified that while the presence of CD8(+) T cells alone was insufficient to predict successful TIL generation, the CD8(+) to FoxP3(+) ratio was predictive with a positive-predictive value (PPV) of 91 % and negative-predictive value (NPV) of 86 %. Incorporation of CD163+ macrophage numbers and CD8:PD-L1 ratio did not improve the PPV. However, the NPV could be improved to 100 % by including the ratio of CD8(+):PD-L1(+) expressing cells. **CONCLUSION:** This is the first study to apply 7-color multispectral immunohistochemistry to analyze the immune environment of tumors from patients with melanoma. Assessment of the data using unsupervised hierarchical clustering identified tumors from which we were unable to generate TIL. If substantiated, this immune profile could be applied to select patients for TIL generation. Additionally, this biomarker profile may also indicate a pre-existing immune response, and serve as a predictive biomarker of patients who will respond to checkpoint blockade. We postulate that

expanding the spectrum of inhibitory cells and molecules assessed using this technique could guide combination immunotherapy treatments and improve response rates.

Ferencik, M., Liu, T., Mayrhofer, T., Puchner, S. B., Lu, M. T., Maurovich-Horvat, P., et al. (2015). Hs-troponin I followed by CT angiography improves acute coronary syndrome risk stratification accuracy and work-up in acute chest pain patients: Results from ROMICAT II trial.

*JACC.Cardiovascular Imaging,*

**OBJECTIVES:** This study compared diagnostic accuracy of conventional troponin/traditional coronary artery disease (CAD) assessment and highly sensitive troponin (hsTn) I/advanced CAD assessment for acute coronary syndrome (ACS) during the index hospitalization. **BACKGROUND:** hsTnI and advanced assessment of CAD using coronary computed tomography angiography (CTA) are promising candidates to improve the accuracy of emergency department evaluation of patients with suspected ACS. **METHODS:** We performed an observational cohort study in patients with suspected ACS enrolled in the ROMICAT II (Rule Out Myocardial Infarction/Ischemia using Computer Assisted Tomography) trial and randomized to coronary CTA who also had hsTnI measurement at the time of the emergency department presentation. We assessed coronary CTA for traditional (no CAD, nonobstructive CAD,  $\geq 50\%$  stenosis) and advanced features of CAD ( $\geq 50\%$  stenosis, high-risk plaque features: positive remodeling, low  $\geq 50\%$  stenosis and high-risk plaque ruled out ACS in patients with intermediate hsTnI ( $n = 87$ , 54.4%; ACS rate 0%), whereas patients with both  $\geq 50\%$  stenosis and high-risk plaque were at high risk ( $n = 13$ , 8.1%; ACS rate 69.2%) and patients with either  $\geq 50\%$  stenosis or high-risk plaque were at intermediate risk for ACS ( $n = 39$ , 24.4%; ACS rate 7.7%). hsTnI/advanced coronary CTA assessment significantly improved the diagnostic accuracy for ACS as compared to conventional troponin/traditional coronary CTA (area under the curve 0.84, 95% confidence interval [CI] 0.80 to .88 vs. 0.74, 95%CI 0.70 to 0.78;  $p < 0.001$ ). **CONCLUSIONS:** hsTnI at the time of presentation followed by early advanced coronary CTA assessment improves the risk stratification and diagnostic accuracy for ACS as compared to conventional troponin and traditional coronary CTA assessment. (Multicenter Study to Rule Out Myocardial Infarction/Ischemia by Cardiac Computed Tomography [ROMICAT-II]; NCT01084239).

Ferguson, B., & Smith, D. G. (2015). Evolutionary history and genetic variation of macaca mulatta and macaca fascicularis. (pp. 17-35) Elsevier Inc.

The geographic distributions of rhesus and cynomolgus macaques exceed those of all other nonhuman primate (NHP) species and encompass regional populations that are genetically distinct. Indian and Chinese rhesus macaques represent the two most divergent regional populations of rhesus macaques, whereas the Indochinese cynomolgus macaque reflects an introgression of Chinese rhesus macaque genes. Genome variant discovery studies have not only informed the evolutionary history of macaques, but also have provided insight into the range of potential functional alleles and diversity among populations. The challenge ahead is to more fully characterize the natural variation within and between macaque species, both to maximize the utility of macaques as models of human disease, as well as to inform their use in the development and testing of pharmacogenetic drug therapies. © 2015 Elsevier Inc. All rights reserved.

Ferrante, J. M., Friedman, A., Shaw, E. K., Howard, J., Cohen, D. J., & Shahidi, L. (2015). Lessons learned designing and using an online discussion forum for care coordinators in primary care. *Qualitative Health Research*,

While an increasing number of researchers are using online discussion forums for qualitative research, few authors have documented their experiences and lessons learned to demonstrate this method's viability and validity in health services research. We comprehensively describe our experiences, from start to finish, of designing and using an asynchronous online discussion forum for collecting and analyzing information elicited from care coordinators in Patient-Centered Medical Homes across the United States. Our lessons learned from each phase, including planning, designing, implementing, using, and ending this private online discussion forum, provide some recommendations for other health services researchers considering this method. An asynchronous online discussion forum is a feasible, efficient, and effective method to conduct a qualitative study, particularly when subjects are health professionals.

Fields, J. M., Fischer, J. I., Anderson, K. L., Mangili, A., Panebianco, N. L., & Dean, A. J. (2015). The ability of renal ultrasound and ureteral jet evaluation to predict 30-day outcomes in patients with

suspected nephrolithiasis. *American Journal of Emergency Medicine*, 33(10), 1402-1406.

**Study objective** We sought to identify findings on bedside renal ultrasound that predicted need for hospitalization in patients with suspected nephrolithiasis. **Methods** A convenience sample of patients with suspected nephrolithiasis was prospectively enrolled and underwent bedside ultrasound of the kidneys and bladder to determine the presence and degree of hydronephrosis and ureteral jets. Sonologists were blinded to any other laboratory and imaging data. Patients were followed up at 30 days by phone call and review of medical records. **Results** Seventy-seven patients with suspected renal colic were included in the analysis. Thirteen patients were admitted. Reasons for admission included intractable pain, infection, or emergent urologic intervention. All 13 patients requiring admission had hydronephrosis present on initial bedside ultrasound. Patients with moderate hydronephrosis had a higher admission rate (36%) than those with mild hydronephrosis (24%),  $P < .01$ . Of patients without hydronephrosis, none required admission within 30 days. The sensitivity and specificity of hydronephrosis for predicting subsequent hospitalization were 100% and 44%, respectively. Loss of the ipsilateral ureteral jet was not significantly associated with subsequent hospital admission and did not improve the predictive value when used in combination with the degree of hydronephrosis. **Conclusions** No patients with suspected renal colic and absence of hydronephrosis on bedside ultrasound required admission within 30 days. Ureteral jet evaluation did not help in prediction of 30-day outcomes and may not be useful in the emergency department management of renal colic. © 2015 Elsevier Inc.

Fleshman, J., Branda, M., Sargent, D. J., Boller, A. M., George, V., Abbas, M., et al. (2015). Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: The ACOSOG Z6051 randomized clinical trial. *Jama*, 314(13), 1346-1355.

**IMPORTANCE:** Evidence about the efficacy of laparoscopic resection of rectal cancer is incomplete, particularly for patients with more advanced-stage disease. **OBJECTIVE:** To determine whether laparoscopic resection is noninferior to open resection, as determined by gross pathologic and histologic evaluation of the resected proctectomy specimen. **DESIGN, SETTING, AND PARTICIPANTS:** A multicenter, balanced, noninferiority, randomized trial enrolled patients between October 2008 and September 2013. The trial was conducted by credentialed surgeons from 35 institutions in the United States and Canada. A total of 486 patients with

clinical stage II or III rectal cancer within 12 cm of the anal verge were randomized after completion of neoadjuvant therapy to laparoscopic or open resection. INTERVENTIONS: Standard laparoscopic and open approaches were performed by the credentialed surgeons. MAIN OUTCOMES AND MEASURES: The primary outcome assessing efficacy was a composite of circumferential radial margin greater than 1 mm, distal margin without tumor, and completeness of total mesorectal excision. A 6% noninferiority margin was chosen according to clinical relevance estimation. RESULTS: Two hundred forty patients with laparoscopic resection and 222 with open resection were evaluable for analysis of the 486 enrolled. Successful resection occurred in 81.7% of laparoscopic resection cases (95% CI, 76.8%-86.6%) and 86.9% of open resection cases (95% CI, 82.5%-91.4%) and did not support noninferiority (difference, -5.3%; 1-sided 95% CI, -10.8% to infinity; P for noninferiority = .41). Patients underwent low anterior resection (76.7%) or abdominoperineal resection (23.3%). Conversion to open resection occurred in 11.3% of patients. Operative time was significantly longer for laparoscopic resection (mean, 266.2 vs 220.6 minutes; mean difference, 45.5 minutes; 95% CI, 27.7-63.4; P < .001). Length of stay (7.3 vs 7.0 days; mean difference, 0.3 days; 95% CI, -0.6 to 1.1), readmission within 30 days (3.3% vs 4.1%; difference, -0.7%; 95% CI, -4.2% to 2.7%), and severe complications (22.5% vs 22.1%; difference, 0.4%; 95% CI, -4.2% to 2.7%) did not differ significantly. Quality of the total mesorectal excision specimen in 462 operated and analyzed surgeries was complete (77%) and nearly complete (16.5%) in 93.5% of the cases. Negative circumferential radial margin was observed in 90% of the overall group (87.9% laparoscopic resection and 92.3% open resection; P = .11). Distal margin result was negative in more than 98% of patients irrespective of type of surgery (P = .91). CONCLUSIONS AND RELEVANCE: Among patients with stage II or III rectal cancer, the use of laparoscopic resection compared with open resection failed to meet the criterion for noninferiority for pathologic outcomes. Pending clinical oncologic outcomes, the findings do not support the use of laparoscopic resection in these patients. TRIAL REGISTRATION: [clinicaltrials.gov](https://clinicaltrials.gov) Identifier: NCT00726622.

Fromme, E. K., Holliday, E. B., Nail, L. M., Lyons, K. S., Hribar, M. R., & Thomas, C. R., Jr. (2015). Computerized patient-reported symptom assessment in radiotherapy: A pilot randomized, controlled trial. *Supportive Care in Cancer : Official Journal of the Multinational Association of*

*Supportive Care in Cancer,*

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.

Gaier, E. D., Boudreault, K., Rizzo, J. F., III, Falardeau, J., & Cestari, D. M. (2015). Atypical optic neuritis. *Current Neurology and Neuroscience Reports*, 15(12)

Classic demyelinating optic neuritis is associated with multiple sclerosis and typically carries a good prognosis for visual recovery. This disorder is well characterized with respect to its presentation and clinical features by baseline data obtained through the optic neuritis treatment trial and numerous other studies. Atypical optic neuritis entails clinical manifestations that deviate from this classic pattern of features. Clinical signs and symptoms that deviate from the

typical presentation should prompt consideration of less common etiologies. Atypical features to consider include lack of pain, simultaneous or near-simultaneous onset, lack of response to or relapse upon tapering from corticosteroids, or optic nerve head or peripapillary hemorrhages. The most important alternative etiologies to consider and the steps towards their respective diagnostic evaluations are suggested for these atypical features. © 2015, Springer Science+Business Media New York.

Gale, M. J., Feng, S., Titus, H. E., Smith, T. B., & Pennesi, M. E. (2016). Interpretation of flood-illuminated adaptive optics images in subjects with retinitis pigmentosa. *Advances in Experimental Medicine and Biology*, 854, 291-297.

The purpose of this study was to correlate features on flood-illuminated adaptive optics (AO) images with color fundus, fundus autofluorescence (FAF) and spectral domain optical coherence tomography (SD-OCT) images in patients with retinitis pigmentosa (RP). We imaged 39 subjects diagnosed with RP using the rtx1(TM) flood-illuminated AO camera from Imagine Eyes (Orsay, France). We observed a correlation between hyper-autofluorescence changes on FAF, disruption of the interdigitation zone (IZ) on SD-OCT and loss of reflective cone profiles on AO. Four main patterns of cone-reflectivity were seen on AO: presumed healthy cone mosaics, hypo-reflective blurred cone-like structures, higher frequency disorganized hyper-reflective spots, and lower frequency hypo-reflective spots. These regions were correlated to progressive phases of cone photoreceptor degeneration observed using SD-OCT and FAF. These results help provide interpretation of en face images obtained by flood-illuminated AO in subjects with RP. However, significant ambiguity remains as to what truly constitutes a cone, especially in areas of degeneration. With further refinements in technology, flood illuminated AO imaging has the potential to provide rapid, standardized, longitudinal and lower cost imaging in patients with retinal degeneration.

Garbati, M. R., Hays, L. E., Rathbun, R. K., Jillette, N., Chin, K., Al-Dhalimy, M., et al. (2015).

Cytokine overproduction and crosslinker hypersensitivity are unlinked in fanconi anemia macrophages. *Journal of Leukocyte Biology*,

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-alpha 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-alpha in response to TLR-activating signals. DNA damaging agents alone did not induce TNF-alpha 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.

Garcia-Aguilar, J., Renfro, L. A., Chow, O. S., Shi, Q., Carrero, X. W., Lynn, P. B., et al. (2015). Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): Results of an open-label, single-arm, multi-institutional, phase 2 trial. *The Lancet.Oncology*,

BACKGROUND: Local excision is an organ-preserving treatment alternative to transabdominal resection for patients with stage I rectal cancer. However, local excision alone is associated with a high risk of local recurrence and inferior survival compared with transabdominal rectal resection. We investigated the oncological and functional outcomes of neoadjuvant chemoradiotherapy and local excision for patients with stage T2N0 rectal cancer. METHODS: We

did a multi-institutional, single-arm, open-label, non-randomised, phase 2 trial of patients with clinically staged T2N0 distal rectal cancer treated with neoadjuvant chemoradiotherapy at 26 American College of Surgeons Oncology Group institutions. Patients with clinical T2N0 rectal adenocarcinoma staged by endorectal ultrasound or endorectal coil MRI, measuring less than 4 cm in greatest diameter, involving less than 40% of the circumference of the rectum, located within 8 cm of the anal verge, and with an Eastern Cooperative Oncology Group performance status of at least 2 were included in the study. Neoadjuvant chemoradiotherapy consisted of capecitabine (original dose 825 mg/m<sup>2</sup> twice daily on days 1-14 and 22-35), oxaliplatin (50 mg/m<sup>2</sup> on weeks 1, 2, 4, and 5), and radiation (5 days a week at 1.8 Gy per day for 5 weeks to a dose of 45 Gy, followed by a boost of 9 Gy, for a total dose of 54 Gy) followed by local excision. Because of adverse events during chemoradiotherapy, the dose of capecitabine was reduced to 725 mg/m<sup>2</sup> twice-daily, 5 days per week, for 5 weeks, and the boost of radiation was reduced to 5.4 Gy, for a total dose of 50.4 Gy. The primary endpoint was 3-year disease-free survival for all eligible patients (intention-to-treat population) and for patients who completed chemotherapy and radiation, and had ypT0, ypT1, or ypT2 tumours, and negative resection margins (per-protocol group). This study is registered with ClinicalTrials.gov, number NCT00114231.

**FINDINGS:** Between May 25, 2006, and Oct 22, 2009, 79 eligible patients were recruited to the trial and started neoadjuvant chemoradiotherapy. Two patients had no surgery and one had a total mesorectal excision. Four additional patients completed protocol treatment, but one had a positive margin and three had ypT3 tumours. Thus, the per-protocol population consisted of 72 patients. Median follow-up was 56 months (IQR 46-63) for all patients. The estimated 3-year disease-free survival for the intention-to-treat group was 88.2% (95% CI 81.3-95.8), and for the per-protocol group was 86.9% (79.3-95.3). Of 79 eligible patients, 23 (29%) had grade 3 gastrointestinal adverse events, 12 (15%) had grade 3-4 pain, and 12 (15%) had grade 3-4 haematological adverse events during chemoradiation. Of the 77 patients who had surgery, six (8%) had grade 3 pain, three (4%) had grade 3-4 haemorrhage, and three (4%) had gastrointestinal adverse events. **INTERPRETATION:** Although the observed 3-year disease free survival was not as high as anticipated, our data suggest that neoadjuvant chemoradiotherapy followed by local excision might be considered as an organ-preserving alternative in carefully

selected patients with clinically staged T2N0 tumours who refuse, or are not candidates for, transabdominal resection. FUNDING: National Cancer Institute and Sanofi-Aventis.

Garg, N., Truong, B., Ku, J. H., Devere, T. S., Ehst, B. D., Blauvelt, A., et al. (2015). A novel, short, and simple screening questionnaire can suggest presence of psoriatic arthritis in psoriasis patients in a dermatology clinic. *Clinical Rheumatology*, 34(10), 1745-1751.

Delaying diagnosis of psoriatic arthritis (PsA) can lead to poor quality of life and disability. The purpose of this study is to identify simple questions for dermatologists to screen psoriasis patients for psoriatic arthritis. Data regarding psoriasis and arthritis were prospectively collected by a questionnaire from all psoriasis patients. Patients with joint-related symptoms were assessed by a rheumatologist for the presence of PsA. Retrospectively, the sensitivity and specificity, positive and negative predictive values, likelihood ratios, and posttest probabilities of various screening questions were calculated to identify the best combination of parameters. Of 517 patients seen in dermatology clinic, 117 (22.63 %) were found to have PsA. Four screening questions ("Do you have a history of joint pain or swelling?" "Do you have stiffness in the morning?" "Have you had X-rays taken of your joints?" "Do you have PsA?") with psoriatic nail changes demonstrated high sensitivity and specificity for predicting PsA. A cutoff of three out of these five parameters correctly classified patients with and without PsA with 86.9 % sensitivity, 71.3 % specificity, 53 % positive predictive value (PPV), 93.6 % negative predictive value (NPV), and area under the curve (AUC) of 0.87. Likelihood ratios for individual parameters varied between 1.6 and 3.7, and with a combination of certain parameters, the posttest probability of PsA was 76 %. This is a preliminary data on a potential screening questionnaire which can help dermatologists quickly screen for PsA. All patients not having evaluated by a rheumatologist could have led to underdiagnosis of PsA and potential misclassification. Psoriasis patients seen at a specialty clinic may introduce a referral bias. © 2014, Clinical Rheumatology.

Gerrah, R., Sunstrom PA-C, R. E., & Hohimer, A. R. (2015). Pretreatment of synthetic vascular grafts with heparin before implantation, a simple technique to reduce the risk of thrombosis. *Vascular*, 23(5), 513-518.

Thrombosis of synthetic grafts commonly used in cardiovascular surgery is a major complication.

We examined whether pretreatment of the graft with heparin reduces the risk of early thrombosis. A circuit was assembled to compare two pairs of shunts simultaneously in the same animal. The study shunts were pretreated with heparin. After 2 hours of circulation, clot formation was evaluated by image analysis techniques. The pretreated grafts had fewer blood clots adhered to the surface by direct visual inspection. The image analysis showed 5 vs. 39 clots, 0.01% vs. 1.8% clotted area, and 62 vs. 5630 clot pixel area between the treated and non-treated grafts respectively,  $p < 0.05$ . Pretreatment of the synthetic graft with heparin prior to implantation reduces the risk of early clot formation. This simple practice might be helpful to prevent initial thrombosis of the graft and later occlusion. © 2014, © The Author(s) 2014.

Gesuete, R., Stevens, S. L., & Stenzel-Poore, M. P. (2016). *Role of circulating immune cells in stroke and preconditioning- induced protection* Springer-Verlag Wien.

Giralt, S., Garderet, L., Durie, B., Cook, G., Gahrton, G., Bruno, B., et al. (2015). American society of blood and marrow transplantation, european society of blood and marrow transplantation, blood and marrow transplant clinical trials network, and international myeloma working group consensus conference on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,

In contrast to the upfront setting in which the role of high-dose therapy with autologous hematopoietic cell transplantation (HCT) as consolidation of a first remission in patients with multiple myeloma (MM) is well established, the role of high-dose therapy with autologous or allogeneic HCT has not been extensively studied in MM patients relapsing after primary therapy. The International Myeloma Working Group together with the Blood and Marrow Transplant Clinical Trials Network, the American Society of Blood and Marrow Transplantation, and the European Society of Blood and Marrow Transplantation convened a meeting of MM experts to: (1) summarize current knowledge regarding the role of autologous or allogeneic HCT in MM patients progressing after primary therapy, (2) propose guidelines for the use of salvage HCT in MM, (3) identify knowledge gaps, (4) propose a research agenda, and (5) develop a collaborative initiative to move the research agenda forward. After reviewing the available data, the expert

committee came to the following consensus statement for salvage autologous HCT: (1) In transplantation-eligible patients relapsing after primary therapy that did NOT include an autologous HCT, high-dose therapy with HCT as part of salvage therapy should be considered standard; (2) High-dose therapy and autologous HCT should be considered appropriate therapy for any patients relapsing after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months; (3) High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT; (4) The role of postsalvage HCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, immune-modulating agents, and oral proteasome inhibitors; (5) Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short (less than 18 months remissions) after primary therapy; and (6) Prospective randomized trials need to be performed to define the role of salvage autologous HCT in patients with MM relapsing after primary therapy comparing it to "best non-HCT" therapy. The expert committee also underscored the importance of collecting enough hematopoietic stem cells to perform 2 transplantations early in the course of the disease. Regarding allogeneic HCT, the expert committee agreed on the following consensus statements: (1) Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT and/or high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase); (2) Allogeneic HCT should be performed in the context of a clinical trial if possible; (3) The role of postallogeneic HCT maintenance therapy needs to be explored in the context of well-designed prospective trials; and (4) Prospective randomized trials need to be performed to define the role salvage allogeneic HCT in patients with MM relapsing after primary therapy.

Gold, R., Hollombe, C., Bunce, A., Nelson, C., Davis, J. V., Cowburn, S., et al. (2015). Study protocol for "study of practices enabling implementation and adaptation in the safety net (SPREAD-NET)": A pragmatic trial comparing implementation strategies. *Implementation Science : IS*, 10(1), 144-015-0333-y.

BACKGROUND: Little research has directly compared the effectiveness of implementation

strategies in any setting, and we know of no prior trials directly comparing how effectively different combinations of strategies support implementation in community health centers. This paper outlines the protocol of the Study of Practices Enabling Implementation and Adaptation in the Safety Net (SPREAD-NET), a trial designed to compare the effectiveness of several common strategies for supporting implementation of an intervention and explore contextual factors that impact the strategies' effectiveness in the community health center setting. METHODS/DESIGN: This cluster-randomized trial compares how three increasingly hands-on implementation strategies support adoption of an evidence-based diabetes quality improvement intervention in 29 community health centers, managed by 12 healthcare organizations. The strategies are as follows: (arm 1) a toolkit, presented in paper and electronic form, which includes a training webinar; (arm 2) toolkit plus in-person training with a focus on practice change and change management strategies; and (arm 3) toolkit, in-person training, plus practice facilitation with on-site visits. We use a mixed methods approach to data collection and analysis: (i) baseline surveys on study clinic characteristics, to explore how these characteristics impact the clinics' ability to implement the tools and the effectiveness of each implementation strategy; (ii) quantitative data on change in rates of guideline-concordant prescribing; and (iii) qualitative data on the "how" and "why" underlying the quantitative results. The outcomes of interest are clinic-level results, categorized using the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework, within an interrupted time-series design with segmented regression models. This pragmatic trial will compare how well each implementation strategy works in "real-world" practices. DISCUSSION: Having a better understanding of how different strategies support implementation efforts could positively impact the field of implementation science, by comparing practical, generalizable methods for implementing clinical innovations in community health centers. Bridging this gap in the literature is a critical step towards the national long-term goal of effectively disseminating and implementing effective interventions into community health centers. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02325531.

Gottlieb, D. H., Maier, A., & Coleman, K. (2015). Evaluation of environmental and intrinsic factors that contribute to stereotypic behavior in captive rhesus macaques (*macaca mulatta*). *Applied Animal Behaviour Science*, 171, 184-191.

Full body repetitive behaviors, known as motor stereotypic behaviors (MSBs), are one of the most commonly seen abnormal behaviors in captive non-human primates, and are frequently used as a behavioral measure of well-being. The main goal of this paper was to examine the role of environmental factors (i.e., foraging enrichment and socialization) and intrinsic factors (i.e., temperament and origin) in the development of MSB in rhesus macaques living in cages. MSB was assessed during short annual observations in which a trained observer recorded a monkey's behavior for 5. min, followed by a 3-min novel object test. Data were collected over 11 years, totaling 9805 observations. We compared MSB for animals with and without foraging enrichment, and across three socialization conditions: full contact pairing, protected contact socialization (partners physically separated by widely spaced bars), and single housing. In addition, we evaluated whether individual differences in response to a novel object and ancestral origin (i.e., China vs. India), predicted MSB expression during the annual observations. Data were analyzed using generalized mixed effects modeling, with the best fitting models chosen using Akaike Information Criterion. Subjects were at lowest risk for MSB when a foraging device was present ( $p < 0.05$ ), and when in full contact social housing ( $p < 0.001$ ). There was no statistically significant difference in MSB between subjects that were single housed and subjects housed in protected contact pairs. In addition, subjects that never touched the novel object were significantly less likely to exhibit MSB than those that touched the object immediately ( $p < 0.001$ ) or within 3. min ( $p < 0.001$ ). Finally, monkeys with some degree of Chinese ancestry were significantly more likely to display MSB than Indian-origin monkeys ( $p < 0.05$ ). These results add to the growing body of literature on factors that can contribute to the development of MSB. © 2015 Elsevier B.V.

Graham, A. M., Buss, C., Rasmussen, J. M., Rudolph, M. D., Demeter, D. V., Gilmore, J. H., et al.

(2015). Implications of newborn amygdala connectivity for fear and cognitive development at 6-months-of-age. *Developmental Cognitive Neuroscience*,

The first year of life is an important period for emergence of fear in humans. While animal models have revealed developmental changes in amygdala circuitry accompanying emerging fear, human neural systems involved in early fear development remain poorly understood. To increase understanding of the neural foundations of human fear, it is important to consider parallel

cognitive development, which may modulate associations between typical development of early fear and subsequent risk for fear-related psychopathology. We, therefore, examined amygdala functional connectivity with rs-fcMRI in 48 neonates (M=3.65 weeks, SD=1.72), and measured fear and cognitive development at 6-months-of-age. Stronger, positive neonatal amygdala connectivity to several regions, including bilateral anterior insula and ventral striatum, was prospectively associated with higher fear at 6-months. Stronger amygdala connectivity to ventral anterior cingulate/anterior medial prefrontal cortex predicted a specific phenotype of higher fear combined with more advanced cognitive development. Overall, findings demonstrate unique profiles of neonatal amygdala functional connectivity related to emerging fear and cognitive development, which may have implications for normative and pathological fear in later years. Consideration of infant fear in the context of cognitive development will likely contribute to a more nuanced understanding of fear, its neural bases, and its implications for future mental health.

Green, S. S. (2015). Ingested and aspirated foreign bodies. *Pediatrics in Review / American Academy of Pediatrics*, 36(10), 430-437.

Hameed, M., Corless, C., George, S., Hornick, J. L., Kakar, S., Lazar, A. J., et al. (2015). Template for reporting results of biomarker testing of specimens from patients with gastrointestinal stromal tumors. *Archives of Pathology and Laboratory Medicine*, 139(10), 1271-1275.

Hanyok, B. T., Howard, L. E., Amling, C. L., Aronson, W. J., Cooperberg, M. R., Kane, C. J., et al. (2015). Is computed tomography a necessary part of a metastatic evaluation for castration-resistant prostate cancer? results from the shared equal access regional cancer hospital database. *Cancer*,

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

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

Harrington, E. K., Dworkin, S., Withers, M., Onono, M., Kwena, Z., & Newmann, S. J. (2015).

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 & Sexuality*, , 1-17.

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.

Hauck, M. J., & Steele, E. A. (2015). Dermis fat graft implantation after unilateral enucleation for retinoblastoma in pediatric patients. *Ophthalmic Plastic and Reconstructive Surgery*, 31(2), 136-138.

PURPOSE: To evaluate the efficacy of dermis fat graft (DFG) as a primary implant technique in pediatric patients requiring unilateral enucleation due to retinoblastoma. METHODS: A retrospective chart review of 14 consecutive pediatric patients who underwent dermis fat graft implantation after unilateral enucleation for retinoblastoma by 1 surgeon (E.A.S.) was performed to evaluate graft efficacy with regard to orbital volume growth and any associated morbidity. Patients who received chemotherapy or external beam radiation were excluded. Demographic information was recorded. Serial MRIs were used to measure orbital volumes to compare the surgical and contralateral orbits over time. The main outcome measure was the difference in bony orbital volume between enucleated and contralateral, uninvolved orbits. Mann-Whitney U test was used to compare orbital volume measurements between surgical and nonsurgical orbits. Correlation testing was performed to determine the effect of age, sex, and follow-up time on the orbital volume changes. RESULTS: There was no statistical difference between the MRI volume measured for surgical and nonsurgical orbits over time. This was the case at all measured time points and for all ages and genders. All patients were under the age of 4 years at the time of surgery. The median difference in orbital volumes between surgical and nonsurgical orbits was -0.095 cm (range -1.26 to 1.01 cm; quartiles -0.32 to 0.07 cm; mean  $\pm$  SD,  $-0.144 \pm 0.0522$  cm; 95% confidence interval, -0.247 to -0.0419 cm). The median follow-up time from surgery date to the most recent clinical examination was 38.5 months (range, 13 to 70 months; quartiles, 28.75 to 45.5 months; mean  $\pm$  standard deviation [SD],  $38.43 \pm 17.21$  months; 95% confidence interval, 29.41 to 47.45 months). CONCLUSIONS: In pediatric patients below 4 years of age with

unilateral retinoblastoma treated with enucleation and primary dermis fat graft implantation, there was no statistically significant difference in bony orbital volume between the surgical and nonsurgical orbits during the follow-up period.

He, W., Tu, J., Huo, Z., Li, Y., Peng, J., Qiu, Z., et al. (2015). Surgical interventions for gastric cancer: A review of systematic reviews. *International Journal of Clinical and Experimental Medicine*, 8(8), 13657-13669.

Aim: To evaluate methodological quality and the extent of concordance among meta-analysis and/or systematic reviews on surgical interventions for gastric cancer (GC). Methods: A comprehensive search of PubMed, Medline, EMBASE, the Cochrane library and the DARE database was conducted to identify the reviews comparing different surgical interventions for GC prior to April 2014. After applying included criteria, available data were summarized and appraised by the Oxman and Guyatt scale. Results: Fifty six reviews were included. Forty five reviews (80.4%) were well conducted, with scores of adapted Oxman and Guyatt scale  $\geq 14$ . The reviews differed in criteria for avoiding bias and assessing the validity of the primary studies. Many primary studies displayed major methodological flaws, such as randomization, allocation concealment, and dropouts and withdrawals. According to the concordance assessment, laparoscopy-assisted gastrectomy (LAG) was superior to open gastrectomy, and laparoscopy-assisted distal gastrectomy was superior to open distal gastrectomy in short-term outcomes. However, the concordance regarding other surgical interventions, such as D1 vs. D2 lymphadenectomy, and robotic gastrectomy vs. LAG were absent. Conclusion: Systematic reviews on surgical interventions for GC displayed relatively high methodological quality. The improvement of methodological quality and reporting was necessary for primary studies. The superiority of laparoscopic over open surgery was demonstrated. But concordance on other surgical interventions was rare, which needed more well-designed RCTs and systematic reviews. © 2015 E-Century Publishing Corporation. All rights reserved.

Heung, M., Faubel, S., Watnick, S., Cruz, D. N., Koyner, J. L., Mour, G., et al. (2015). Outpatient dialysis for patients with AKI: A policy approach to improving care. *Clinical Journal of the American Society of Nephrology*, 10(10), 1868-1874.

The rate of AKI requiring dialysis has increased significantly over the past decade in the United States. At the same time, survival from AKI seems to be improving, and thus, more patients with AKI are surviving to discharge while still requiring dialysis. Currently, the options for providing outpatient dialysis in patients with AKI are limited, particularly after a 2012 revised interpretation of the Centers for Medicare and Medicaid Services guidelines, which prohibited Medicare reimbursement for acute dialysis at ESRD facilities. This article provides a historical perspective on outpatient dialysis management of patients with AKI, reviews the current clinical landscape of care for these patients, and highlights key areas of knowledge deficit. Lastly, policy changes that have the opportunity to significantly improve the care of this at-risk population are suggested. © 2015 by the American Society of Nephrology.

Hofmann, M. E., & Andresen, M. C. (2015). Vanilloids selectively sensitize thermal glutamate release from TRPV1 expressing solitary tract afferents. *Neuropharmacology*, *101*, 401-411.

Vanilloids, high temperature, and low pH activate the transient receptor potential vanilloid type 1 (TRPV1) receptor. In spinal dorsal root ganglia, co-activation of one of these gating sites on TRPV1 sensitized receptor gating by other modes. Here in rat brainstem slices, we examined glutamate synaptic transmission in nucleus of the solitary tract (NTS) neurons where most cranial primary afferents express TRPV1, but TRPV1 sensitization is unknown. Electrical shocks to the solitary tract (ST) evoked EPSCs (ST-EPSCs). Activation of TRPV1 with capsaicin (100 nM) increased spontaneous EPSCs (sEPSCs) but inhibited ST-EPSCs. High concentrations of the ultra-potent vanilloid resiniferatoxin (RTX, 1 nM) similarly increased sEPSC rates but blocked ST-EPSCs. Lowering the RTX concentration to 150 pM modestly increased the frequency of the sEPSCs without causing failures in the evoked ST-EPSCs. The sEPSC rate increased with raising bath temperature to 36 degrees C. Such thermal responses were larger in 150 pM RTX, while the ST-EPSCs remained unaffected. Vanilloid sensitization of thermal responses persisted in TTX but was blocked by the TRPV1 antagonist capsazepine. Our results demonstrate that multimodal activation of TRPV1 facilitates sEPSC responses in more than the arithmetic sum of the two activators, i.e. co-activation sensitizes TRPV1 control of spontaneous glutamate release. Since action potential evoked glutamate release is unaltered, the work provides evidence for cooperativity in gating TRPV1 plus a remarkable separation of calcium mechanisms governing the

independent vesicle pools responsible for spontaneous and evoked release at primary afferents in the NTS.

Holtzinger, A., Streeter, P. R., Sarangi, F., Hillborn, S., Niapour, M., Ogawa, S., et al. (2015). New markers for tracking endoderm induction and hepatocyte differentiation from human pluripotent stem cells. *Development (Cambridge, England)*,

The efficient generation of hepatocytes from human pluripotent stem cells (hPSCs) requires the induction of a proper endoderm population, broadly characterized by the expression of the cell surface marker CXCR4. Strategies to identify and isolate endoderm subpopulations predisposed to the liver fate do not exist. In this study, we generated mouse monoclonal antibodies against hESC-derived definitive endoderm with the goal of identifying cell surface markers that can be used to track the development of this germ layer and its specification to a hepatic fate. Through this approach, we identified two endoderm-specific antibodies, HDE1 and HDE2 that stain different stages of endoderm development and distinct derivative cell types. HDE1 marks a definitive endoderm population with high hepatic potential whereas staining of HDE2 tracks with developing hepatocyte progenitors and hepatocytes. When used in combination, the staining patterns of these antibodies enable one to optimize endoderm induction and hepatic specification from any hPSC line.

Horikawa, M., Miyayama, S., Irie, T., Kaji, T., & Arai, Y. (2015). Development of conventional transarterial chemoembolization for hepatocellular carcinomas in Japan: Historical, strategic, and technical review. *American Journal of Roentgenology*, 205(4), 764-773.

**OBJECTIVE.** This article reviews the development of transarterial chemoembolization (TACE) in Japan, particularly ethiodized oil-based conventional TACE, from historical, strategic, and technical points of view. We also present the current status of standardized conventional TACE.

**CONCLUSION.** Conventional TACE has been developed toward a more-selective and hemodynamic-conscious method, along with technical innovation and knowledge accumulation.

Standardization of this method is necessary for further scientific evaluation. © American Roentgen Ray Society.

Horner-Johnson, W., Dobbertin, K., Kulkarni-Rajasekhara, S., Beilstein-Wedel, E., & Andresen, E. M. (2015). Food insecurity, hunger, and obesity among informal caregivers. *Preventing Chronic Disease, 12*, E170.

INTRODUCTION: Increasing numbers of US residents rely on informal caregiving from friends and family members. Caregiving can have substantial health and financial impacts on caregivers. This study addressed whether those impacts include adverse nutritional states. Specifically, we examined household food insecurity, individual hunger, and obesity among caregivers compared with noncaregivers. METHODS: We analyzed 2012 Behavioral Risk Factor Surveillance System data from Oregon. The Caregiving Module was administered to a random subset of 2,872 respondents. Module respondents included 2,278 noncaregivers and 594 caregivers providing care or assistance to a friend or family member with a health problem or disability. We used multivariable logistic regression to assess associations between caregiving status and each of our dependent variables. RESULTS: Caregivers had significantly greater odds of reporting household food insecurity (odds ratio [OR] = 2.10, P = .003) and personal hunger (OR = 2.89, P = .002), even after controlling for income and other correlates of food insecurity. There were no significant differences in obesity between caregivers and noncaregivers. CONCLUSION: Caregiving is associated with increased risk of food insecurity and hunger in Oregon, suggesting that careful attention to the nutritional profile of households with family caregivers is needed in this population.

Huda, F. A., Ahmed, A., Ford, E. R., & Johnston, H. B. (2015). Strengthening health systems capacity to monitor and evaluate programmes targeted at reducing abortion-related maternal mortality in Jessore district, Bangladesh. *BMC Health Services Research, 15*(1), 426-015-1115-6.

BACKGROUND: Abortion related deaths as a proportion of maternal mortality appears to have fallen dramatically in Bangladesh from 5 % in 2001 to 1 % in 2010. Yet complications from menstrual regulation (MR) and unsafe abortion continue to cause deleterious health, economic and social consequences for women in the country. METHODS: This quasi experimental design study with a baseline (January to December 2008) and an endline survey (August to October 2009) was conducted in 69 public, private, and NGO sector health facilities in Jessore district of Bangladesh with the objective of adapting and implementing a set of process indicators,

specifically to supplement the indicators for monitoring emergency obstetric care interventions. At the baseline, we collected retrospective data from all 69 health facilities that provided MR, legal abortion or post-abortion care (PAC), by reviewing their last one year's records. Three months after introducing the safe menstrual regulation and abortion care (SMRAC) model, endline data was collected. Signal function (critical services that facilities must perform in order to prevent and treat abortion complications) analysis was used to characterize facilities as providing basic care, comprehensive care, or neither. Facility mapping, and records on services provided and complications treated were used to further characterize service availability and to describe service use and quality. RESULTS: No facilities fulfilled criteria for 'comprehensive' care at either the baseline or end line while only one met the 'basic' criteria during the endline of the project. Recommended uterine evacuation technology, manual vacuum aspiration (MVA) was used for 100.0 % of MR clients but only for 8.0 % or fewer PAC patients. MR clients were 37.5 times more likely than PAC patients to leave facilities with a contraceptive method (75.0 % vs. 2.0 %). CONCLUSION: Persistent use of older uterine evacuation technologies was observed when recommended techniques were widely available in the facilities. Notable gaps were identified in providing post-abortion contraceptive services for women treated for PAC. By systematic implementation of the SMRAC model, health systems can track and measure progress and gaps in their implementation and identify strategies for further reduction of abortion-related morbidity and mortality in Bangladesh.

Huen, A., & Fett, N. (2015). An enormous tumor in a patient with clinically amyopathic dermatomyositis: Answer. *The American Journal of Dermatopathology*, 37(11), 870.

Huen, A., & Fett, N. (2015). An enormous tumor in a patient with clinically amyopathic dermatomyositis: Challenge. *The American Journal of Dermatopathology*, 37(11), 852-853.

Hunter, J. G. (2015). Welcome associate editor zsolt balogh. *World Journal of Surgery*, 39(10), 2375-015-3172-8.

Imber, B. S., Braunstein, S. E., Wu, F. Y., Nabavizadeh, N., Boehling, N., Weinberg, V. K., et al. (2015). Clinical outcome and prognostic factors for central neurocytoma: Twenty year

institutional experience. *Journal of Neuro-Oncology*,

Central neurocytomas are uncommon intraventricular neoplasms whose optimal management remains controversial due to their rarity. We assessed outcomes for a historical cohort of neurocytoma patients and evaluated effects of tumor atypia, size, resection extent, and adjuvant radiotherapy. Progression-free survival (PFS) was measured by Kaplan-Meier and Cox proportional hazards methods. A total of 28 patients (15 males, 13 females) were treated between 1995 and 2014, with a median age at diagnosis of 26 years (range 5-61). Median follow-up was 62.2 months and 3 patients were lost to follow-up postoperatively. Thirteen patients experienced recurrent/progressive disease and 2-year PFS was 75 % (95 % CI 53-88 %). Two-year PFS was 48 % for MIB-1 labeling >4 % versus 90 % for 80 % resection was 83 versus 67 % for 4 % is predictive of poorer outcome and our data suggest that adjuvant radiotherapy after STR may improve PFS. Most patients requiring salvage therapy will be stabilized and multiple modalities can be effectively utilized.

Jacobs, P. G., & Kaye, J. A. (2015). Ubiquitous real-world sensing and audiology-based health informatics. *Journal of the American Academy of Audiology*, 26(9), 777-783.

BACKGROUND: Hearing impairment and hearing rehabilitation strategies have historically been studied within the confines of a sound booth under controlled experimental conditions. The real world is quite different from the clinical setting and it is important to study how a person with hearing impairment interacts with the world both with and without a hearing assist intervention. A person's ability to hear enables them to communicate and to effectively interact with the world. If a person suffers from hearing impairment, we might anticipate that they could become more disengaged from the world, more socially isolated, potentially depressed, and have additional comorbidities such as cognitive and physical impairment. Indeed, prior research has shown that hearing impairment is associated with social isolation, decreased functional ability and mobility, fall risk, diabetes, and cognitive impairment. However, nearly all of the work that has been done in this area of assessing the impact of hearing impairment on a person's social, cognitive, and physical health has been done through clinical tests or self-report studies using questionnaires and surveys that attempt to objectively quantify various aspects of health. Unfortunately, clinical tests, questionnaires, and surveys oftentimes inaccurately assess a person's true social,

cognitive, and physical health. Only when a person is observed in their natural living environment can a more accurate assessment of health be obtained. The ability to assess hearing health, social engagement, cognitive, and physical health in natural living environments is becoming possible with the advent of ubiquitous sensing capabilities. PURPOSE: Here we discuss some of the work that has been done by our group and others that may be of use to the field of audiology e-health. The purpose of this article is not to present new experimental data, but rather to describe a new method of using advanced in-home sensing techniques to better understand how hearing diagnostics, interventions, and rehabilitation influence the lives and behaviors of patients.

Jacobs, P. G., Resalat, N., El Youssef, J., Reddy, R., Branigan, D., Preiser, N., et al. (2015).

Incorporating an exercise detection, grading, and hormone dosing algorithm into the artificial pancreas using accelerometry and heart rate. *Journal of Diabetes Science and Technology*, 9(6), 1175-1184.

In this article, we present several important contributions necessary for enabling an artificial endocrine pancreas (AP) system to better respond to exercise events. First, we show how exercise can be automatically detected using body-worn accelerometer and heart rate sensors. During a 22 hour overnight inpatient study, 13 subjects with type 1 diabetes wearing a Zephyr accelerometer and heart rate monitor underwent 45 minutes of mild aerobic treadmill exercise while controlling their glucose levels using sensor-augmented pump therapy. We used the accelerometer and heart rate as inputs into a validated regression model. Using this model, we were able to detect the exercise event with a sensitivity of 97.2% and a specificity of 99.5%. Second, from this same study, we show how patients' glucose declined during the exercise event and we present results from in silico modeling that demonstrate how including an exercise model in the glucoregulatory model improves the estimation of the drop in glucose during exercise. Last, we present an exercise dosing adjustment algorithm and describe parameter tuning and performance using an in silico glucoregulatory model during an exercise event.

Jany, P. L., Agosta, G. E., Benko, W. S., Eickhoff, J. C., Keller, S. R., Koehler, W., et al. (2015). CSF and blood levels of GFAP in alexander disease(1,2,3). *Eneuro*, 2(5), 10.1523/ENEURO.0080-15.2015. eCollection 2015 Sep.

Alexander disease is a rare, progressive, and generally fatal neurological disorder that results from dominant mutations affecting the coding region of GFAP, the gene encoding glial fibrillary acidic protein, the major intermediate filament protein of astrocytes in the CNS. A key step in pathogenesis appears to be the accumulation of GFAP within astrocytes to excessive levels. Studies using mouse models indicate that the severity of the phenotype correlates with the level of expression, and suppression of GFAP expression and/or accumulation is one strategy that is being pursued as a potential treatment. With the goal of identifying biomarkers that indirectly reflect the levels of GFAP in brain parenchyma, we have assayed GFAP levels in two body fluids in humans that are readily accessible as biopsy sites: CSF and blood. We find that GFAP levels are consistently elevated in the CSF of patients with Alexander disease, but only occasionally and modestly elevated in blood. These results provide the foundation for future studies that will explore whether GFAP levels can serve as a convenient means to monitor the progression of disease and the response to treatment.

Jarvik, J. G., Comstock, B. A., James, K. T., Avins, A. L., Bresnahan, B. W., Deyo, R. A., et al. (2015).

Lumbar imaging with reporting of epidemiology (LIRE)-protocol for a pragmatic cluster randomized trial. *Contemporary Clinical Trials*,

BACKGROUND: Diagnostic imaging is often the first step in evaluating patients with back pain and likely functions as a "gateway" to a subsequent cascade of interventions. However, lumbar spine imaging frequently reveals incidental findings among normal, pain-free individuals suggesting that treatment of these "abnormalities" may not be warranted. Our prior work suggested that inserting the prevalence of imaging findings in patients without back pain into spine imaging reports may reduce subsequent interventions. We are now conducting a pragmatic cluster randomized clinical trial to test the hypothesis that inserting this prevalence data into lumbar spine imaging reports for studies ordered by primary care providers will reduce subsequent spine-related interventions. METHODS/DESIGN: We are using a stepped wedge design that sequentially randomizes 100 primary care clinics at four health systems to receive either standard lumbar spine imaging reports, or reports containing prevalence data for common imaging findings in patients without back pain. We capture all outcomes passively through the electronic medical record. Our primary outcome is spine-related intervention intensity based on

Relative Value Units (RVUs) during the following year. Secondary outcomes include subsequent prescriptions for opioid analgesics and cross-sectional lumbar spine re-imaging. DISCUSSION: If our study shows that adding prevalence data to spine imaging reports decreases subsequent back-related RVUs, this intervention could be easily generalized and applied to other kinds of testing, as well as other conditions where incidental findings may be common. Our study also serves as a model for cluster randomized trials that are minimal risk and highly pragmatic.

Jia, Y., & Huang, D. (2015). Noninvasive ocular angiography by optical coherence tomography. (pp. 63-71) Springer Berlin Heidelberg.

Diabetic retinopathy, age-related macular degeneration, and glaucoma are all associated with impaired circulation. Noninvasive assessment of ocular circulation would be very powerful for understanding and diagnosing these eye diseases. Using high-speed optical coherence tomography (OCT), we developed a new OCT angiography algorithm called split-spectrum amplitude-decorrelation angiography (SSADA) for imaging ocular microcirculation. Here, the system and theory of this novel OCT angiography technique are reviewed; its capabilities for imaging retinal, choroidal, and optic nerve head blood flow are demonstrated; and its limitation is discussed. © Springer-Verlag Berlin Heidelberg 2015.

Jonker, S. S., & Louey, S. (2015). Endocrine and other physiologic modulators of perinatal cardiomyocyte endowment. *The Journal of Endocrinology*,

Immature contractile cardiomyocytes proliferate to rapidly increase cell number, establishing cardiomyocyte endowment in the perinatal period. Developmental changes in cellular maturation, size and attrition further contribute to cardiac anatomy. These physiological processes occur concomitant with a changing hormonal environment as the fetus prepares itself for the transition to extrauterine life. There are complex interactions between endocrine, hemodynamic and nutritional regulators of cardiac development. Birth has been long assumed to be the trigger for major differences between the fetal and postnatal cardiomyocyte growth patterns, but investigations in normally growing sheep and rodents suggest this may not be entirely true; in sheep, these differences are initiated before birth, while in rodents they occur after birth. The aim of this review is to draw together our understanding of the temporal regulation of these signals

and cardiomyocyte responses relative to birth. Further, we consider how these dynamics are altered in stressed and suboptimal intrauterine environments.

Kaneshiro, B., Edelman, A., Dash, C., Pandhare, J., Soli, F. M., & Jensen, J. T. (2015). Effect of oral contraceptives and doxycycline on endometrial MMP-2 and MMP-9 activity. *Contraception*,  
OBJECTIVES: To describe the effect of combined oral contraceptives (COCs) on matrix metalloproteinases MMP-2 and MMP-9 activity and compare MMP activity in women taking a COC with or without doxycycline. STUDY DESIGN: Subjects (n=20) underwent endometrial biopsies (1) in the late luteal phase of a baseline cycle prior to initiating COCs, (2) on days 19-21 while taking COCs in a standard 28-day cycle (7-day hormone-free interval) and (3) on days 26-28 while taking active COCs continuously for a 28-day cycle. During the continuous COC cycle, they were randomized to receive daily subantimicrobial dose doxycycline 40mg or placebo. RESULTS: Compared to baseline, COC treatment increased MMP-2 ( $p<.001$ ) and MMP-9 ( $p<.001$ ). MMP activity was lower in subjects taking a COC with doxycycline compared to those receiving placebo although only significantly lower for MMP-2 latent form ( $p=.002$ ). CONCLUSIONS: Unscheduled bleeding with COCs may be the result of increased endometrial MMPs. Sample size limitations prevent us from determining how doxycycline affects MMP activity in COC users.

Kang, B. P., Slosberg, E., Snodgrass, S., Lebedinsky, C., Berry, D. A., Corless, C. L., et al. (2015). The signature program: Bringing the protocol to the patient. *Clinical Pharmacology and Therapeutics*, 98(2), 124-126.

Early-phase clinical development in oncology has evolved dramatically with the deciphering of the human genome in 2004. Genomic analysis and the tools identifying genetically disrupted pathways within a patient's tumor have been a driving force for personalized medicine and for the development of highly targeted novel therapies. Tumors are often genetically heterogeneous, with multiple concurrent genetic abnormalities. On the other hand, tumors arising from different tissues may share identical molecular drivers.

Kaul, S. (2015). Assessment of myocardial collateral blood flow with contrast echocardiography. *Korean Circulation Journal*, 45(5), 351-356.

Humans have pre-formed collateral vessels that enlarge with ischemia. In addition, new vessels

can be formed within ischemic zones from pre-formed endocardial arcades of vessels providing rich collateral flow. Collateral flow under resting conditions (if >25% of normal) is enough to maintain myocardial viability, but may be insufficient to prevent myocardial ischemia under stress. Coronary angiography is a poor tool for collateral flow assessment. Myocardial contrast echocardiography is arguably the gold standard for experimental and clinical measurement of collateral flow. This review describes several experimental and clinical studies that highlight the importance of the collateral circulation in coronary artery disease.

Keiser, M. S., Kordasiewicz, H., & McBride, J. (2015). Gene suppression strategies for dominantly inherited neurodegenerative diseases: Lessons from huntington's disease and spinocerebellar ataxia. *Human Molecular Genetics*,  
RNA targeting approaches are emerging as viable therapeutics that offer an alternative method to modulate traditionally "undrugable" targets. In the case of dominantly inherited neurodegenerative diseases, gene suppression strategies can target the underlying cause of these intractable disorders. Polyglutamine diseases are caused by CAG expansions in discrete genes, making them ideal candidates for gene suppression therapies. Here, we discuss the current state of gene suppression approaches for Huntington's disease and the spinocerebellar ataxias, including the use of antisense oligonucleotides (ASOs), short interfering RNAs (siRNAs), as well as viral vector mediated delivery of short hairpin RNAs (shRNAs) and artificial microRNAs (miRNAs). We focus on lessons learned from pre-clinical studies investigating gene suppression therapies for these disorders, particularly in rodent models of disease and in non-human primates. In animal models, recent advances in gene suppression technologies have not only prevented disease progression in a number of cases, but have also reversed existing disease, providing evidence that reducing the expression of disease-causing genes may be of benefit in symptomatic patients. Both allele- and non-allele specific approaches to gene suppression have made great strides over the past decade showing efficacy and safety in both small and large animal models. Advances in delivery techniques allow for broad and durable suppression of target genes, and have been validated in non-human primates and in some cases, are currently being evaluated in human patients. Finally, we discuss the challenges of developing and delivering gene suppression constructs into the CNS and recent advances of potential therapeutics into the clinic.

Kelly, M. P., Zebala, L. P., Kim, H. J., Sciubba, D. M., Smith, J. S., Shaffrey, C. I., et al. (2015).

Effectiveness of preoperative autologous blood donation for protection against allogeneic blood exposure in adult spinal deformity surgeries: A propensity-matched cohort analysis. *Journal of Neurosurgery.Spine*, , 1-7.

**OBJECT** The goal of this study was to examine the effectiveness of preoperative autologous blood donation (PABD) in adult spinal deformity (ASD) surgery. **METHODS** Patients undergoing single-stay ASD reconstructions were identified in a multicenter database. Patients were divided into groups according to PABD (either PABD or NoPABD). Propensity weighting was used to create matched cohorts of PABD and NoPABD patients. Allogeneic (ALLO) exposure, autologous (AUTO) wastage (unused AUTO), and complication rates were compared between groups. **RESULTS** Four hundred twenty-eight patients were identified as meeting eligibility criteria. Sixty patients were treated with PABD, of whom 50 were matched to 50 patients who were not treated with PABD (NoPABD). Nearly one-third of patients in the PABD group (18/60, 30%) did not receive any autologous transfusion and donated blood was wasted. In 6 of these cases (6/60, 10%), patients received ALLO blood transfusions without AUTO. In 9 cases (9/60, 15%), patients received ALLO and AUTO blood transfusions. Overall rates of transfusion of any type were similar between groups (PABD 70% [42/60], NoPABD 75% [275/368],  $p = 0.438$ ). Major and minor in-hospital complications were similar between groups (Major PABD 10% [6/60], NoPABD 12% [43/368],  $p = 0.537$ ; Minor PABD 30% [18/60], NoPABD 24% [87/368],  $p = 0.499$ ). When controlling for potential confounders, PABD patients were more likely to receive some transfusion (OR 15.1, 95% CI 2.1-106.7). No relationship between PABD and ALLO blood exposure was observed, however, refuting the concept that PABD is protective against ALLO blood exposure. In the matched cohorts, PABD patients were more likely to sustain a major perioperative cardiac complication (PABD 8/50 [16%], NoPABD 1/50 [2%],  $p = 0.046$ ). No differences in rates of infection or wound-healing complications were observed between cohorts. **CONCLUSIONS** Preoperative autologous blood donation was associated with a higher probability of perioperative transfusions of any type in patients with ASD. No protective effect of PABD against ALLO blood exposure was observed, and no risk of perioperative infectious complications was observed in patients exposed to ALLO blood only. The benefit of PABD in patients with ASD remains undefined.

Kendrick, S., Tus, K., Wright, G., Jaffe, E. S., Rosenwald, A., Campo, E., et al. (2015). Diffuse large B-cell lymphoma cell-of-origin classification using the Lymph2Cx assay in the context of BCL2 and MYC expression status. *Leukemia & Lymphoma*, , 1-4.

Kim, C., & Prasad, V. (2015). Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US food and drug administration approvals. *JAMA Internal Medicine*, , 1-2.

King, L. A., Peterson, D. S., Mancini, M., Carlson-Kuhta, P., Fling, B. W., Smulders, K., et al. (2015). Do cognitive measures and brain circuitry predict outcomes of exercise in parkinson disease: A randomized clinical trial. *BMC Neurology*, 15, 218-015-0474-2.

BACKGROUND: There is emerging research detailing the relationship between balance/gait/falls and cognition. Imaging studies also suggest a link between structural and functional changes in the frontal lobe (a region commonly associated with cognitive function) and mobility. People with Parkinson's disease have important changes in cognitive function that may impact rehabilitation efficacy. Our underlying hypothesis is that cognitive function and frontal lobe connections with the basal ganglia and brainstem posture/locomotor centers are responsible for postural deficits in people with Parkinson's disease and play a role in rehabilitation efficacy. The purpose of this study is to 1) determine if people with Parkinson's disease can improve mobility and/or cognition after partaking in a cognitively challenging mobility exercise program and 2) determine if cognition and brain circuitry deficits predict responsiveness to exercise rehabilitation.

METHODS/DESIGN: This study is a randomized cross-over controlled intervention to take place at a University Balance Disorders Laboratory. The study participants will be people with Parkinson's disease who meet inclusion criteria for the study. The intervention will be 6 weeks of group exercise (case) and 6 weeks of group education (control). The exercise is a cognitively challenging program based on the Agility Boot Camp for people with PD. The education program is a 6-week program to teach people how to better live with a chronic disease. The primary outcome measure is the MiniBESTest and the secondary outcomes are measures of mobility, cognition and neural imaging. DISCUSSION: The results from this study will further our understanding of the relationship between cognition and mobility with a focus on brain circuitry

as it relates to rehabilitation potential. TRIAL REGISTRATION: This trial is registered at clinical trials.gov ( NCT02231073 ).

Klag, K. A., & Horton, W. A. (2015). Advances in treatment of achondroplasia and osteoarthritis.

*Human Molecular Genetics,*

Achondroplasia (ACH) is the prototype and most common of the human chondrodysplasias. It results from gain-of-function mutations that exaggerate the signal output of the fibroblast growth factor receptor 3 (FGFR3), a receptor tyrosine kinase that negatively regulates growth plate activity and linear bone growth. Several approaches to reduce FGFR3 signaling by blocking receptor activation or inhibiting downstream signals have been proposed. Five show promise in preclinical mouse studies. Two candidate therapies target the extracellular domain of FGFR3. The first is a decoy receptor that competes for activating ligands. The second is a synthetic blocking peptide that prevents ligands from binding and activating FGFR3. Two established drugs, statins and meclozine, improve growth of ACH mice. The strongest candidate therapy employs an analog of C-type natriuretic peptide (CNP), which antagonizes the mitogen-activated-protein (MAP) kinase pathway downstream of the FGFR3 receptor and may also act independently in the growth plate. Only the CNP analog has reached clinical trials. Preliminary results of Phase 2 studies show a substantial increase in growth rate of ACH children after six months of therapy with no serious adverse effects. A challenge for drug therapy in ACH is targeting agents to the avascular growth plate. The application of gene therapy in osteoarthritis offers insights because it faces similar technical obstacles. Major advances in gene therapy include the emergence of recombinant adeno-associated virus as the vector of choice, capsid engineering to target vectors to specific tissues, and development of methods to direct vectors to articular chondrocytes.

Klein, E. (2015). Informed consent in implantable BCI research: Identifying risks and exploring meaning. *Science and Engineering Ethics,*

Implantable brain-computer interface (BCI) technology is an expanding area of engineering research now moving into clinical application. Ensuring meaningful informed consent in implantable BCI research is an ethical imperative. The emerging and rapidly evolving nature of implantable BCI research makes identification of risks, a critical component of informed consent,

a challenge. In this paper, 6 core risk domains relevant to implantable BCI research are identified-short and long term safety, cognitive and communicative impairment, inappropriate expectations, involuntariness, affective impairment, and privacy and security. Work in deep brain stimulation provides a useful starting point for understanding this core set of risks in implantable BCI. Three further risk domains-risks pertaining to identity, agency, and stigma-are identified. These risks are not typically part of formalized consent processes. It is important as informed consent practices are further developed for implantable BCI research that attention be paid not just to disclosing core research risks but exploring the meaning of BCI research with potential participants.

Klyuchnikov, E., Bacher, U., Woo Ahn, K., Carreras, J., Kroger, N. M., Hari, P. N., et al. (2015). Long-term survival outcomes of reduced-intensity allogeneic or autologous transplantation in relapsed grade 3 follicular lymphoma. *Bone Marrow Transplantation*,  
Grade 3 follicular lymphoma (FL) has aggressive clinical behavior. To evaluate the optimal first transplantation approach in relapsed/refractory grade 3 FL patients, we compared the long-term outcomes after allogeneic (allo-) vs autologous hematopoietic cell transplantation (auto-HCT) in the rituximab era. A total of 197 patients undergoing first reduced-intensity conditioning (RIC) allo-HCT or first auto-HCT during 2000-2012 were included. Rituximab-naive patients were excluded. Allo-HCT recipients were younger, more heavily pretreated and had a longer interval between diagnosis and HCT. The 5-year probabilities of non-relapse mortality (NRM), relapse/progression, PFS and overall survival (OS) for auto-HCT vs allo-HCT groups were 4% vs 27% ( $P<0.001$ ), 61% vs 20% ( $P<0.001$ ), 36% vs 51% ( $P=0.07$ ) and 59% vs 54% ( $P=0.7$ ), respectively. On multivariate analysis, auto-HCT was associated with reduced risk of NRM (relative risk (RR)=0.20;  $P=0.001$ ). Within the first 11 months post HCT, auto- and allo-HCT had similar risks of relapse/progression and PFS. Beyond 11 months, auto-HCT was associated with higher risk of relapse/progression (RR=21.3;  $P=0.003$ ) and inferior PFS (RR=3.2;  $P=0.005$ ). In the first 24 months post HCT, auto-HCT was associated with improved OS (RR=0.42;  $P=0.005$ ), but in long-time survivors (beyond 24 months) it was associated with inferior OS (RR=3.6;  $P=0.04$ ). RIC allo-HCT as the first transplant approach can provide improved PFS and OS, in

long-term survivors. Bone Marrow Transplantation advance online publication, 5 October 2015; doi:10.1038/bmt.2015.223.

Ko, A. L., Ozpinar, A., Raskin, J. S., Magill, S. T., Raslan, A. M., & Burchiel, K. J. (2015). Correlation of preoperative MRI with the long-term outcomes of dorsal root entry zone lesioning for brachial plexus avulsion pain. *Journal of Neurosurgery*, , 1-9.

**OBJECT** Lesioning of the dorsal root entry zone (DREZotomy) is an effective treatment for brachial plexus avulsion (BPA) pain. The role of preoperative assessment with MRI has been shown to be unreliable for determining affected levels; however, it may have a role in predicting pain outcomes. Here, DREZotomy outcomes are reviewed and preoperative MRI is examined as a possible prognostic factor. **METHODS** A retrospective review was performed of an institutional database of patients who had undergone brachial plexus DREZ procedures since 1995. Preoperative MRI was examined to assess damage to the DREZ or dorsal horn, as evidenced by avulsion of the DREZ or T2 hyperintensity within the spinal cord. Phone interviews were conducted to assess the long-term pain outcomes. **RESULTS** Between 1995 and 2012, 27 patients were found to have undergone cervical DREZ procedures for BPA. Of these, 15 had preoperative MR images of the cervical spine available for review. The outcomes were graded from 1 to 4 as poor (no significant relief), good (more than 50% pain relief), excellent (more than 75% pain relief), or pain free, respectively. Overall, DREZotomy was found to be a safe, efficacious, and durable procedure for relief of pain due to BPA. The initial success rate was 73%, which declined to 66% at a median follow-up time of 62.5 months. Damage to the DREZ or dorsal horn was significantly correlated with poorer outcomes ( $p = 0.02$ ). The average outcomes in patients without MRI evidence of DREZ or dorsal horn damage was significantly higher than in patients with such damage (3.67 vs 1.75, t-test;  $p = 0.001$ ). A longer duration of pain prior to operation was also a significant predictor of treatment success ( $p = 0.004$ ). **CONCLUSIONS** Overall, the DREZotomy procedure has a 66% chance of achieving meaningful pain relief on long-term follow-up. Successful pain relief is associated with the lack of damage to the DREZ and dorsal horn on preoperative MRI.

Lam, R., Li, H., & Nock, M. L. (2015). Assessment of G6PD screening program in premature infants in a NICU. *Journal of Perinatology : Official Journal of the California Perinatal Association*,  
OBJECTIVE: Targeted screening for glucose-6-phosphate dehydrogenase deficiency (G6PDdef) using fluorescent spot test (FST) is done in our newborn nursery (NN) and now in our NICU. Premature infants have higher G6PD levels than term infants. FST may result in under diagnosis of G6PDdef in preterms. We sought to determine if FST is appropriate for diagnosis of G6PDdef at <35 weeks and assess screening in NICU. STUDY DESIGN: Retrospective chart review of male, inborn infants <35 weeks in NICU from 2008 to 2011. Difference in G6PDdef incidence <5% between NN and NICU was acceptable for equivalence. RESULTS: Out of 679 subjects, 442 were screened for G6PDdef and 11.3% had abnormal results. Binomial testing comparing 11.3% (95% confidence interval (CI) 8.5 to 14.6) incidence of G6PDdef in NICU and reported incidence in NN (11%) demonstrated no difference. 12.2% of Black/African American males were not screened. CONCLUSION: FST is appropriate for screening all at-risk newborns. A number of at-risk premature males were not screened. *Journal of Perinatology* advance online publication, 22 October 2015; doi:10.1038/jp.2015.129.

Lamprecht, B., Soriano, J. B., Studnicka, M., Kaiser, B., Vanfleteren, L. E., Gnatiuc, L., et al. (2015). Determinants of underdiagnosis of COPD in national and international surveys. *Chest*, *148*(4), 971-985.  
Background: COPD ranks within the top three causes of mortality in the global burden of disease, yet it remains largely underdiagnosed. We assessed the underdiagnosis of COPD and its determinants in national and international surveys of general populations. Methods: We analyzed representative samples of adults aged  $\geq 40$  years randomly selected from well-defined administrative areas worldwide (44 sites from 27 countries). Postbronchodilator FEV<sub>1</sub> /FVC < lower limit of normal (LLN) was used to define chronic airflow limitation consistent with COPD. Undiagnosed COPD was considered when participants had postbronchodilator FEV<sub>1</sub> /FVC < LLN but were not given a diagnosis of COPD. Results: Among 30,874 participants with a mean age of 56 years, 55.8% were women, and 22.9% were current smokers. Population prevalence of (spirometrically defined) COPD ranged from 3.6% in Barranquilla, Colombia, to 19.0% in Cape Town, South Africa. Only 26.4% reported a previous lung function test, and only 5.0% reported a

previous diagnosis of COPD, whereas 9.7% had a postbronchodilator FEV<sub>1</sub> /FVC < LLN. Overall, 81.4% of (spirometrically defined) COPD cases were undiagnosed, with the highest rate in Ile-Ife, Nigeria (98.3%) and the lowest rate in Lexington, Kentucky (50.0%). In multivariate analysis, a greater probability of underdiagnosis of COPD was associated with male sex, younger age, never and current smoking, lower education, no previous spirometry, and less severe airflow limitation. Conclusions: Even with substantial heterogeneity in COPD prevalence, COPD underdiagnosis is universally high. Because effective management strategies are available for COPD, spirometry can help in the diagnosis of COPD at a stage when treatment will lead to better outcomes and improved quality of life. © 2015 American College of Chest Physicians.

Landfear, S. M., Tran, K. D., & Sanchez, M. A. (2015). Flagellar membrane proteins in kinetoplastid parasites. *IUBMB Life*, 67(9), 668-676.

All kinetoplastid parasites, including protozoa such as *Leishmania* species, *Trypanosoma brucei*, and *Trypanosoma cruzi* that cause devastating diseases in humans and animals, are flagellated throughout their life cycles. Although flagella were originally thought of primarily as motility organelles, flagellar functions in other critical processes, especially in sensing and signal transduction, have become more fully appreciated in the recent past. The flagellar membrane is a highly specialized subdomain of the surface membrane, and flagellar membrane proteins are likely to be critical components for all the biologically important roles of flagella. In this review, we summarize recent discoveries relevant to flagellar membrane proteins in these parasites, including the identification of such proteins, investigation of their biological functions, and mechanisms of selective trafficking to the flagellar membrane. Prospects for future investigations and current unsolved problems are highlighted. © 2015 IUBMB Life. © 2015 International Union of Biochemistry and Molecular Biology.

Lawrenson, K., Iversen, E. S., Tyrer, J., Weber, R. P., Concannon, P., Hazelett, D. J., et al. (2015).

Common variants at the CHEK2 gene locus and risk of epithelial ovarian cancer. *Carcinogenesis*, 36(11), 1341-1353.

Genome-wide association studies have identified 20 genomic regions associated with risk of epithelial ovarian cancer (EOC), but many additional risk variants may exist. Here, we evaluated

associations between common genetic variants [single nucleotide polymorphisms (SNPs) and indels] in DNA repair genes and EOC risk. We genotyped 2896 common variants at 143 gene loci in DNA samples from 15 397 patients with invasive EOC and controls. We found evidence of associations with EOC risk for variants at FANCA, EXO1, E2F4, E2F2, CREB5 and CHEK2 genes ( $P \leq 0.001$ ). The strongest risk association was for CHEK2 SNP rs17507066 with serous EOC ( $P = 4.74 \times 10^{-7}$ ). Additional genotyping and imputation of genotypes from the 1000 genomes project identified a slightly more significant association for CHEK2 SNP rs6005807 ( $r^2$  with rs17507066 = 0.84, odds ratio (OR) 1.17, 95% CI 1.11-1.24,  $P = 1.1 \times 10^{-7}$ ). We identified 293 variants in the region with likelihood ratios of less than 1:100 for representing the causal variant. Functional annotation identified 25 candidate SNPs that alter transcription factor binding sites within regulatory elements active in EOC precursor tissues. In The Cancer Genome Atlas dataset, CHEK2 gene expression was significantly higher in primary EOCs compared to normal fallopian tube tissues ( $P = 3.72 \times 10^{-8}$ ). We also identified an association between genotypes of the candidate causal SNP rs12166475 ( $r^2 = 0.99$  with rs6005807) and CHEK2 expression ( $P = 2.70 \times 10^{-8}$ ). These data suggest that common variants at 22q12.1 are associated with risk of serous EOC and CHEK2 as a plausible target susceptibility gene.

Lazelle, R. A., McCully, B. H., Terker, A. S., Himmerkus, N., Blankenstein, K., Mutig, K., et al. (2015).

Renal deletion of 12 kDa FK506-binding protein attenuates tacrolimus-induced hypertension.

*Journal of the American Society of Nephrology : JASN*,

Tacrolimus is a widely used immunosuppressive drug that inhibits the phosphatase calcineurin when bound to the 12 kDa FK506-binding protein (FKBP12). When this binding occurs in T cells, it leads to immunosuppression. Tacrolimus also causes side effects, however, such as hypertension and hyperkalemia. Previously, we reported that tacrolimus stimulates the renal thiazide-sensitive sodium chloride cotransporter (NCC), which is necessary for the development of hypertension. However, it was unclear if tacrolimus-induced hypertension resulted from tacrolimus effects in renal epithelial cells directly or in extrarenal tissues, and whether inhibition of calcineurin was required. To address these questions, we developed a mouse model in which FKBP12 could be deleted along the nephron. FKBP12 disruption alone did not cause phenotypic effects. When treated with tacrolimus, however, BP and the renal abundance of phosphorylated

NCC were lower in mice lacking FKBP12 along the nephron than in control mice. Mice lacking FKBP12 along the nephron also maintained a normal relationship between plasma potassium levels and the abundance of phosphorylated NCC with tacrolimus treatment. In cultured cells, tacrolimus inhibited dephosphorylation of NCC. Together, these results suggest that tacrolimus causes hypertension predominantly by inhibiting calcineurin directly in cells expressing NCC, indicating thiazide diuretics may be particularly effective for lowering BP in tacrolimus-treated patients with hypertension.

Leal, K., & Mochida, S. (2015). Regulation of active zone  $Ca^{2+}$  channel. (pp. 195-220) Springer Japan.

At the presynaptic active zone,  $Ca^{2+}$  influx through voltage-gated CaV2 channels triggers fast, synchronous neurotransmitter release from synaptic vesicles. Synaptic vesicles localized to release sites are tightly coupled with presynaptic CaV2 channels whereby neurotransmitter release is proportional to the  $Ca^{2+}$  current, or the  $Ca^{2+}$  concentration, with the third or fourth power. CaV2 channel activity is regulated directly or indirectly by multiple mechanisms through protein-protein interactions, before and after synaptic vesicle exocytosis, resulting in fine-tuning of  $Ca^{2+}$  entry that effectively modulates basal neurotransmitter release and underlies presynaptic short-term plasticity. Presynaptic active zone proteins form a large complex, which tether CaV2 channels, dock and prime synaptic vesicles at release sites, and possess regulatory function. CaV2 channel modulation, which is upstream of synaptic vesicle exocytosis, that leads to changes in  $Ca^{2+}$  influx provides a powerful and efficient way to regulate synaptic transmission. In this chapter, we review progress toward understanding the cellular and molecular mechanisms that modulate the activity of  $Ca^{2+}$  channels at the presynaptic active zone. A remaining challenge is to understand how these processes work together to shape synaptic transmission and synaptic plasticity. © Springer Japan 2015.

LeBlanc, E. S., & Chou, R. (2015). Vitamin D supplements and the risk of falls-reply. *JAMA Internal Medicine*, 175(10), 1724.

Lee, B., Diaz, G. A., Rhead, W., Lichter-Konecki, U., Feigenbaum, A., Berry, S. A., et al. (2015). Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. *Genetics in Medicine*, 17(7), 561-568.

**Purpose:**The aim of this study was to examine predictors of ammonia exposure and hyperammonemic crises in patients with urea cycle disorders.**Methods:**The relationships between fasting ammonia, daily ammonia exposure, and hyperammonemic crises were analyzed in >100 patients with urea cycle disorders.**Results:**Fasting ammonia correlated strongly with daily ammonia exposure ( $r = 0.764$ ;  $P < 0.0001$ ), respectively. The relationship between ammonia and hyperammonemic crisis risk seemed to be independent of treatment, age, urea cycle disorder subtype, dietary protein intake, or blood urea nitrogen. Fasting glutamine correlated weakly with daily ammonia exposure assessed as 24-hour area under the curve and was not a significant predictor of hyperammonemic crisis.**Conclusion:**Fasting ammonia correlates strongly and positively with daily ammonia exposure and with the risk and rate of hyperammonemic crises, suggesting that patients with urea cycle disorder may benefit from tight ammonia control.*Genet Med* 17 7, 561-568. © 2015 American College of Medical Genetics and Genomics.

Lee, C. S., Gelow, J. M., Mudd, J. O., Green, J. K., Hiatt, S. O., Chien, C., et al. (2015). Profiles of self-care management versus consulting behaviors in adults with heart failure. *European Journal of Cardiovascular Nursing : Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology*, 14(1), 63-72.

**INTRODUCTION:** Patients with heart failure (HF) vary in their ability to respond to symptoms when they occur. The goal of this study was to classify common patterns of symptom response behaviors among adults with HF and identify biobehavioral determinants thereof. **METHODS:** Consulting behaviors (i.e. contacting a provider for guidance) were measured using the European Heart Failure Self-care Behavior Scale consulting behaviors subscale, and self-care management (i.e. recognizing and engaging in self-initiated treatment of symptoms) was measured with the Self-Care of HF Index self-care management scale in a prospective cohort study. Latent class mixture modeling was used to identify distinct profiles of consulting and of self-care management behaviors. **RESULTS:** The mean age ( $n=146$ ) was  $57 \pm 13$  years, 30% were female, and 59% had class III/IV HF. Two distinct profiles of consulting behaviors (novice and expert) and three distinct profiles of self-care management (novice, inconsistent and expert) were identified. There was a weak association between profiles of consulting behaviors and self-care management

(Kendall's tau-b=0.211). Higher levels of anxiety were associated with worse consulting behaviors (beta=1.67+/-0.60) and worse self-care management (beta= -5.82+/-3.12) and lower odds of exhibiting expert level consulting behaviors (odds ratio (OR)=0.50; 95% confidence interval (CI)=0.26-0.95) and self-care management (OR=0.47; 95% CI=0.24-0.92) (all p<0.05). Higher levels of physical symptoms were associated with better self-care management (beta=0.50+/-0.12; OR =1.02, 95% CI=1.00-1.05; both p<0.05). CONCLUSIONS: Expertise in consulting behaviors does not necessarily confer expertise in symptom self-care management and vice versa. Physical and psychological symptoms are strong determinants of symptom response behaviors.

Lee, J. S., DuBois, S. G., Coccia, P. F., Bleyer, A., Olin, R. L., & Goldsby, R. E. (2015). Increased risk of second malignant neoplasms in adolescents and young adults with cancer. *Cancer*,

BACKGROUND: The authors describe the incidence and characteristics of secondary malignant neoplasms (SMNs) in adolescent and young adult (AYA) cancer survivors compared with those in younger and older cancer survivors. METHODS: Children aged  $\geq 40$  years at the time of primary diagnosis who were reported as cancer survivors in the Surveillance, Epidemiology, and End Results (SEER) program between 1973 and 2011 were compared in this population-based analysis. The primary analysis was the risk that an SMN would occur  $\geq 5$  years after the original diagnosis for patients who had the more common AYA cancers (leukemia, lymphoma, testicular malignancy, ovarian malignancy, melanoma, and cancers of the thyroid, breast, soft tissue, or bone). The standardized incidence ratio (SIR), absolute excess risk (AER), and cumulative incidence of SMN for the selected cancers were assessed. The risk of SMN for the entire cohort also was analyzed. RESULTS: Of the 148,558 AYA survivors who were diagnosed with a selected cancer, 7384 developed an SMN 5 years after their original diagnosis. The SIRs (95% confidence intervals [CIs]) were 1.58 (95% CI, 1.55-1.62) for AYAs, 4.26 (95% CI, 3.77-4.80) for children, and 1.10 (95% CI, 1.09-1.11) for older adults, and the AERs were 22.9, 16.6, and 14.7, respectively. The cumulative incidence of SMN at 30 years was 13.9% for the AYA group. The most common SMNs in AYAs were breast cancer, gastrointestinal cancer, genital cancers, and melanoma. AYAs who had received radiation therapy had a higher cumulative incidence of SMN. CONCLUSIONS: AYAs who survive cancer for more than 5 years have a higher

relative risk of SMN compared with the general population and have a higher absolute risk of SMN compared with younger or older cancer survivors. *Cancer* 2015. (c) 2015 American Cancer Society.

LeMond, L., Mai, T., Broberg, C. S., Muralidaran, A., & Burchill, L. J. (2015). Heart failure in adult congenital heart disease: Nonpharmacologic treatment strategies. *Cardiology Clinics*, 33(4), 589-598.

In early stages, heart failure (HF) in adult congenital heart disease (ACHD) remains an elusive diagnosis. Many ACHD patients seem well-compensated owing to chronic physical and psychological adaptations. HF biomarkers and cardiopulmonary exercise tests are often markedly abnormal, although patients report stable health and good quality of life. Treatment differs from acquired HF. Evidence for effective drug therapy in ACHD-related HF is lacking. Residual ventricular, valvular, and vascular abnormalities contribute to HF pathophysiology, leading to an emphasis on nonpharmacologic treatment strategies. This article reviews emerging perspectives on nonpharmacologic treatment strategies, including catheter-based interventions, surgical correction, and palliative care.

Lewis, A. D., & Prongay, K. (2015). Basic physiology of macaca mulatta. (pp. 87-113) Elsevier Inc.

The rhesus macaque (. *Macaca mulatta*) is an Asian Old World nonhuman primate species frequently used in biomedical research, predominately in the study of neuroscience, infectious disease, immunology, and reproductive physiology. They are medium sized, have relatively stout bodies, and exhibit moderate sexual dimorphism. The average weight of males is 7.7. kg and of females is 5.3. kg. In the wild, they live in multimale/multifemale groups. Females form dominance hierarchies based on matrilineal kinship. They are seasonal breeders of relatively low fecundity, with a single infant produced per pregnancy. Gestation is 165 days and sexual maturity is reached at 3-5 years of age in females and 4-6 years of age in males. In this chapter, cardiovascular, respiratory, neurologic, reproductive, immunologic, and gastrointestinal function, as well as methods of assessment and normal values, are reviewed. © 2015 Elsevier Inc. All rights reserved.

Li, S., Nie, E. H., Yin, Y., Benowitz, L. I., Tung, S., Vinters, H. V., et al. (2015). GDF10 is a signal for axonal sprouting and functional recovery after stroke. *Nature Neuroscience*,  
Stroke produces a limited process of neural repair. Axonal sprouting in cortex adjacent to the infarct is part of this recovery process, but the signal that initiates axonal sprouting is not known. Growth and differentiation factor 10 (GDF10) is induced in peri-infarct neurons in mice, non-human primates and humans. GDF10 promotes axonal outgrowth in vitro in mouse, rat and human neurons through TGFbetaRI and TGFbetaRII signaling. Using pharmacogenetic gain- and loss-of-function studies, we found that GDF10 produced axonal sprouting and enhanced functional recovery after stroke; knocking down GDF10 blocked axonal sprouting and reduced recovery. RNA sequencing from peri-infarct cortical neurons revealed that GDF10 downregulated PTEN, upregulated PI3 kinase signaling and induced specific axonal guidance molecules. Using unsupervised genome-wide association analysis of the GDF10 transcriptome, we found that it was not related to neurodevelopment, but may partially overlap with other CNS injury patterns. Thus, GDF10 is a stroke-induced signal for axonal sprouting and functional recovery.

Lieberman, D. A. (2015). The electronic health record paradox: Observations of a GI consultant. *Digestive Diseases and Sciences*, 60(11), 3167-3169.

Lieberman, D. A. (2015). GRG profiles: David A. lieberman. *Digestive Diseases and Sciences*, 60(11), 3162-3166.

Lind, E. F., Millar, D. G., Dissanayake, D., Savage, J. C., Grimshaw, N. K., Kerr, W. G., et al. (2015). miR-155 upregulation in dendritic cells is sufficient to break tolerance in vivo by negatively regulating SHIP1. *Journal of Immunology (Baltimore, Md.: 1950)*,  
TLR-induced maturation of dendritic cells (DCs) leads to the production of proinflammatory cytokines as well as the upregulation of various molecules involved in T cell activation. These are believed to be the critical events that account for the induction of the adaptive immune response. In this study, we have examined the role of miR-155 in DC function and the induction of immunity. Using a model in which the transfer of self-Ag-pulsed, TLR-matured DCs can induce a functional CD8 T cell response and autoimmunity, we find that DCs lacking miR-155 have an impaired ability to break immune tolerance. Importantly, transfer of self- Ag-pulsed DCs

overexpressing miR-155 was sufficient to break tolerance in the absence of TLR stimuli. Although these unstimulated DCs induced T cell function *in vivo*, there was no evidence for the upregulation of costimulatory ligands or cytokine secretion. Further analysis showed that miR-155 influenced the level of the phosphatase SHIP1 in DCs and that the lack of SHIP1 in DCs was sufficient to break T cell tolerance *in vivo*, again in the absence of TLR-induced DC maturation. Our study demonstrates that the overexpression of miR-155 in DCs is a critical event that is alone sufficient to break self-tolerance and promote a CD8-mediated autoimmune response *in vivo*. This process is independent of the induction of conventional DC maturation markers, indicating that miR-155 regulation of SHIP represents a unique axis that regulates DC function *in vivo*.

Linhoff, M. W., Garg, S. K., & Mandel, G. (2015). A high-resolution imaging approach to investigate chromatin architecture in complex tissues. *Cell*, *163*(1), 246-255.

We present ChromATin, a quantitative high-resolution imaging approach for investigating chromatin organization in complex tissues. This method combines analysis of epigenetic modifications by immunostaining, localization of specific DNA sequences by FISH, and high-resolution segregation of nuclear compartments using array tomography (AT) imaging. We then apply this approach to examine how the genome is organized in the mammalian brain using female Rett syndrome mice, which are a mosaic of normal and *Mecp2*-null cells. Side-by-side comparisons within the same field reveal distinct heterochromatin territories in wild-type neurons that are altered in *Mecp2*-null nuclei. Mutant neurons exhibit increased chromatin compaction and a striking redistribution of the H4K20me3 histone modification into pericentromeric heterochromatin, a territory occupied normally by MeCP2. These events are not observed in every neuronal cell type, highlighting ChromATin as a powerful *in situ* method for examining cell-type-specific differences in chromatin architecture in complex tissues.

Liu, L., Gao, S. S., Bailey, S. T., Huang, D., Li, D., & Jia, Y. (2015). Automated choroidal neovascularization detection algorithm for optical coherence tomography angiography. *Biomedical Optics Express*, *6*(9), 3564-3576.

Optical coherence tomography angiography has recently been used to visualize choroidal

neovascularization (CNV) in participants with age-related macular degeneration. Identification and quantification of CNV area is important clinically for disease assessment. An automated algorithm for CNV area detection is presented in this article. It relies on denoising and a saliency detection model to overcome issues such as projection artifacts and the heterogeneity of CNV. Qualitative and quantitative evaluations were performed on scans of 7 participants. Results from the algorithm agreed well with manual delineation of CNV area.

Lo, J. O., Shaffer, B. L., Allen, A. J., Little, S. E., Cheng, Y. W., & Caughey, A. B. (2015). Intrahepatic cholestasis of pregnancy and timing of delivery. *Journal of Maternal-Fetal and Neonatal Medicine*, 28(18), 2254-2258.

Objective: We examined the morbidities from delivery at earlier gestational ages versus intrauterine fetal demise (IUFD) for women with intrahepatic cholestasis of pregnancy (ICP) to determine the optimal gestational age for delivery. Methods: A decision-analytic model was created to compare delivery at 35 through 38 weeks gestation for different delivery strategies: (1) empiric steroids; (2) steroids if fetal lung maturity (FLM) negative; (3) wait a week and retest if FLM negative; or (4) deliver immediately. Literature review identified 18 studies that estimated IUFD in ICP; we used the mean rate, 1.74%, and assumed a uniform distribution from 34 to 40 weeks gestation. Large cohort data was used to calculate neonatal morbidity rates at each gestational age. Maternal and neonatal quality-adjusted life years (QALYs) were combined. Univariate sensitivity and Monte Carlo analyses were performed to test for robustness. Results: Immediate delivery at 36 weeks without FLM testing and steroid administration was the optimal strategy as compared to delivery at 36 weeks with steroids (+47 QALYs) and as compared to immediate delivery at 35 weeks (+210 QALYs). Our results were robust up to a 30% increase in the rate of IUFD. Conclusion: Immediate delivery at 36 weeks in women with ICP is the optimal delivery strategy. © 2014 Informa UK Ltd.

Luchtman, D. W., Chee, M. J., Doslikova, B., Marks, D. L., Baracos, V. E., & Colmers, W. F. (2015). Defense of elevated body weight setpoint in diet-induced obese rats on low energy diet is mediated by loss of melanocortin sensitivity in the paraventricular hypothalamic nucleus. *PLoS One*, 10(10), e0139462.

Some animals and humans fed a high-energy diet (HED) are diet-resistant (DR), remaining as lean as individuals who were naive to HED. Other individuals become obese during HED exposure and subsequently defend the obese weight (Diet-Induced Obesity- Defenders, DIO-D) even when subsequently maintained on a low-energy diet. We hypothesized that the body weight setpoint of the DIO-D phenotype resides in the hypothalamic paraventricular nucleus (PVN), where anorexigenic melanocortins, including melanotan II (MTII), increase presynaptic GABA release, and the orexigenic neuropeptide Y (NPY) inhibits it. After prolonged return to low-energy diet, GABA inputs to PVN neurons from DIO-D rats exhibited highly attenuated responses to MTII compared with those from DR and HED-naive rats. In DIO-D rats, melanocortin-4 receptor expression was significantly reduced in dorsomedial hypothalamus, a major source of GABA input to PVN. Unlike melanocortin responses, NPY actions in PVN of DIO-D rats were unchanged, but were reduced in neurons of the ventromedial hypothalamic nucleus; in PVN of DR rats, NPY responses were paradoxically increased. MTII-sensitivity was restored in DIO-D rats by several weeks' refeeding with HED. The loss of melanocortin sensitivity restricted to PVN of DIO-D animals, and its restoration upon prolonged refeeding with HED suggest that their melanocortin systems retain the ability to up- and downregulate around their elevated body weight setpoint in response to longer-term changes in dietary energy density. These properties are consistent with a mechanism of body weight setpoint.

Lugli, G., Cohen, A. M., Bennett, D. A., Shah, R. C., Fields, C. J., Hernandez, A. G., et al. (2015).

Plasma exosomal miRNAs in persons with and without alzheimer disease: Altered expression and prospects for biomarkers. *PLoS One*, 10(10), e0139233.

To assess the value of exosomal miRNAs as biomarkers for Alzheimer disease (AD), the expression of microRNAs was measured in a plasma fraction enriched in exosomes by differential centrifugation, using Illumina deep sequencing. Samples from 35 persons with a clinical diagnosis of AD dementia were compared to 35 age and sex matched controls. Although these samples contained less than 0.1 microgram of total RNA, deep sequencing gave reliable and informative results. Twenty miRNAs showed significant differences in the AD group in initial screening (miR-23b-3p, miR-24-3p, miR-29b-3p, miR-125b-5p, miR-138-5p, miR-139-5p, miR-141-3p, miR-150-5p, miR-152-3p, miR-185-5p, miR-338-3p, miR-342-3p, miR-342-5p, miR-548at-5p, miR-659-

5p, miR-3065-5p, miR-3613-3p, miR-3916, miR-4772-3p, miR-5001-3p), many of which satisfied additional biological and statistical criteria, and among which a panel of seven miRNAs were highly informative in a machine learning model for predicting AD status of individual samples with 83-89% accuracy. This performance is not due to over-fitting, because a) we used separate samples for training and testing, and b) similar performance was achieved when tested on technical replicate data. Perhaps the most interesting single miRNA was miR-342-3p, which was a) expressed in the AD group at about 60% of control levels, b) highly correlated with several of the other miRNAs that were significantly down-regulated in AD, and c) was also reported to be down-regulated in AD in two previous studies. The findings warrant replication and follow-up with a larger cohort of patients and controls who have been carefully characterized in terms of cognitive and imaging data, other biomarkers (e.g., CSF amyloid and tau levels) and risk factors (e.g., apoE4 status), and who are sampled repeatedly over time. Integrating miRNA expression data with other data is likely to provide informative and robust biomarkers in Alzheimer disease.

Ma, J., Strub, P., Lv, N., Xiao, L., Camargo, C. A., Jr, Buist, A. S., et al. (2015). Pilot randomised trial of a healthy eating behavioural intervention in uncontrolled asthma. *The European Respiratory Journal*,

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

promising clinical benefits for better asthma control and functional status among adults with uncontrolled asthma. A full-scale efficacy trial is warranted.

Madden, J. R., Apg. Vaughn, E. A., Northouse, B., Tong, S., Dorneman, L. A., Foreman, N. K., et al. (2015). Benefits of using an early palliative care intervention in pediatric oncology: Quality of life and cost savings related to home delivery of cisplatin. *Journal of Hospice and Palliative Nursing*, 17(4), 319-324.

Early palliative care (PC) interventions can foster effective symptom management during oncology treatments. Children with cancer are an appropriate population to receive early PC interventions to minimize suffering and foster quality of life during oncology treatments. Delivery of cisplatin along with posthydration (PH) intravenous fluids (IVFs) is an example of an early PC intervention for children diagnosed with standard risk medulloblastoma. In this study, we performed a retrospective chart review to evaluate the impact of outpatient delivery of cisplatin and PH IVF on target outcomes (renal function, ototoxicity, and health care costs) for 45 pediatric patients with standard risk medulloblastoma. Evaluation of physical outcomes revealed (a) no significant changes in serum creatinine, (b) no signs of hemorrhagic cystitis or renal insufficiency, and (c) no significant increase in signs of ototoxicity. Evaluation of health care costs revealed a reduction in the number of required hospital admissions for pediatric patients receiving outpatient cisplatin and PH IVF. In summary, PH IVF after delivery of cisplatin seems to be a potentially effective early PC intervention that may benefit the pediatric oncology patient by preserving renal function, reducing the risk of ototoxicity, and reducing health care costs because of the decreased number of hospital admissions related to outpatient delivery of cisplatin treatments. © 2015, Lippincott Williams and Wilkins. All rights reserved.

Mahadevan, U., & Matro, R. (2015). In reply. *Obstetrics and Gynecology*, 126(5), 1109.

Mancini, M., Chiari, L., Holmstrom, L., Salarian, A., & Horak, F. B. (2015). Validity and reliability of an IMU-based method to detect APAs prior to gait initiation. *Gait & Posture*,  
Anticipatory postural adjustments (APAs) prior to gait initiation have been largely studied in traditional, laboratory settings using force plates under the feet to characterize the displacement of the center of pressure. However clinical trials and clinical practice would benefit from a

portable, inexpensive method for characterizing APAs. Therefore, the main objectives of this study were (1) to develop a novel, automatic IMU-based method to detect and characterize APAs during gait initiation and (2) to measure its test-retest reliability. Experiment I was carried out in the laboratory to determine the validity of the IMU-based method in 10 subjects with PD (OFF medication) and 12 control subjects. Experiment II was carried out in the clinic, to determine test-retest reliability of the IMU-based method in a different set of 17 early-to-moderate, treated subjects with PD (tested ON medication) and 17 age-matched control subjects. Results showed that gait initiation characteristics (both APAs and 1st step) detected with our novel method were significantly correlated to the characteristics calculated with a force plate and motion analysis system. The size of APAs measured with either inertial sensors or force plate was significantly smaller in subjects with PD than in control subjects ( $p < 0.05$ ). Test-retest reliability for the gait initiation characteristics measured with inertial sensors was moderate-to-excellent ( $0.56 < ICC < 0.82$ ) for both groups. Our findings support the feasibility of automatically characterizing postural preparation and gait initiation with body-worn inertial sensors that would be practical for unsupervised clinical and home settings.

Manhart, R., & Rich, P. (2015). Nail psoriasis. *Clinical and Experimental Rheumatology*, 33(5 Suppl 93), 7-13.

Nail psoriasis affects nearly 80% of patients with plaque psoriasis and is even more prevalent in patients with psoriatic arthritis. Nail psoriasis is not simply a cosmetic problem but one that affects the structure and function of the nail, resulting in negative psychological effects. The first level in management of nail psoriasis is patient education. The hierarchy of nail psoriasis therapy begins with topical medication followed by devices, intralesional injections, and small molecules. For nail psoriasis patients unresponsive to these treatments, and especially in patients with severe plaque psoriasis, biologics are safe and effective options.

Marino, M., Bailey, S. R., Gold, R., Hoopes, M. J., O'Malley, J. P., Huguet, N., et al. (2015). Receipt of preventive services after oregon's randomized medicaid experiment. *American Journal of Preventive Medicine*,

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.

Mark, A. G., Wolf, M., Edelman, A., & Castleman, L. (2015). What can obstetrician/gynecologists do to support abortion access? *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics*, 131 Suppl 1, S53-5.

Unsafe abortion causes approximately 13% of all maternal deaths worldwide, with higher rates in areas where abortion access is restricted. Because safe abortion is so low risk, if all women who needed an abortion could access safe care, this rate would drop dramatically. As women's health providers and advocates, obstetrician/gynecologists can support abortion access. By delivering high-quality, evidence-based care ourselves, supporting other providers who perform abortion, helping women who access abortion in the community, providing second-trimester care, and improving contraceptive uptake, we can decrease morbidity and mortality from unsafe abortion.

Markiewicz, M. R., Bell, R. B., Bui, T. G., Dierks, E. J., Ruiz, R., Gelesko, S., et al. (2015). Survival of microvascular free flaps in mandibular reconstruction: A systematic review and meta-analysis. *Microsurgery*, 35(7), 576-587.

**Background** Free tissue transfer is commonly used in the reconstruction of post-ablative defects of the mandible. Due to lack of statistical power, comparing the survival of various free flaps, even in large studies, is challenging. The purpose of this study was to perform a meta-analysis comparing the survival of the most commonly used free flaps for mandibular reconstruction.

**Methods** We searched PubMed, EMBASE, and SCOPUS for relevant studies. A meta-analysis using the Peto one-step odds ratio (OR) with 95% confidence intervals (CI) was used to compare the pooled survival of the most commonly used free flaps for mandibular reconstruction. **Results** Of the 25,303 studies reviewed, 17 were selected for data extraction. A total of 1,221 subjects received 1,262 free flaps. Sixty-five free flaps failed. The pooled survival of all free flaps used for mandibular reconstruction was 94.8%. The deep circumflex iliac artery (DCIA) flap was associated with a seven-fold increase in failure when compared to the radial forearm free flap (Peto OR 7.40; 95% CI 1.38, 39.75, P = 0.02). There was no difference in survival when comparing other commonly used free flaps. **Conclusions** The results of this study suggest that free flap reconstruction of the mandible is highly successful. With the exception of the increased survival of the radial forearm when compared to the DCIA, there is no difference in recipient site survival when comparing various free flaps for mandibular reconstruction. © 2015 Wiley Periodicals, Inc.

Martim, G. C., Detomini, T. R., Schuquel, I. T., Radovanovic, E., Pfeifer, C. S., & Giroto, E. M. (2014).

A urethane-based multimethacrylate mixture and its use in dental composites with combined high-performance properties. *Dental Materials : Official Publication of the Academy of Dental Materials*, 30(2), 155-163.

**OBJECTIVES:** To synthesize and characterize different molar weight urethane multimethacrylates with a single stage (one-pot) procedure. To prepare and characterize the properties of related composites. **METHODS:** Two methacrylate precursors were initially synthesized. Then, these precursors and the multimethacrylate system formed by their coupling were characterized by FTIR and <sup>1</sup>H NMR. The final product was used as a matrix (with TEGDMA and SiO<sub>2</sub> silanized

microparticles) in the preparation of composites and their physical and mechanical properties were compared to those of a bis-GMA-based resin. Water sorption and solubility measurements of the composites were also performed. RESULTS: FTIR and NMR suggested that the proposed synthesis route yields a mixture of mainly urethane-di, -tri, and tetramethacrylates. The composites presented low polymerization shrinkage (e.g. 1.88+/-0.08% for a resin with 70% of SiO<sub>2</sub>) and high flexural strength (e.g. 124.74+/-9.68 MPa for a resin with 65% of SiO<sub>2</sub>) when compared to the bis-GMA based resin and other composites found to date. Water sorption and solubility results show that the composites were deemed compliant with ISO 4049 requirements. SIGNIFICANCE: The mixture containing different molar weight of urethane multimethacrylates showed to be an excellent substitute for bis-GMA, achieving an equilibrium of properties (unlike reports elsewhere which show the enhancement of some parameters in detriment to others) and composites with low polymerization shrinkage, suitable microhardness and degree of conversion, and up to standard water sorption/solubility and flexural strength.

Mascarenhas, R., & Zaman, A. (2015). Appropriate use of beta blockers in cirrhosis. *Current Hepatitis Reports*, 14(3), 243-249.

Cirrhosis of the liver from various etiologies is a leading cause of morbidity and mortality in developing countries and industrialized nations alike. Beta blockers have been used for primary and secondary prophylaxis to prevent the initial episode of bleeding as well as rebleeding from gastroesophageal varices for several decades. However, the side effects of nonselective beta blockers preclude their use in all patients with cirrhosis. Recent evidence suggests that the use of beta blockers in patients with decompensated cirrhosis and refractory ascites may be contraindicated. The purpose of this review is to describe the appropriate use of beta blockers in cirrhosis taking into account emerging data. © Springer Science+Business Media New York 2015.

Matloub, Y., Stork, L., Asselin, B., Hunger, S. P., Borowitz, M., Jones, T., et al. (2015). Outcome of children with standard-risk T-lineage acute lymphoblastic leukemia-comparison among different treatment strategies. *Pediatric Blood & Cancer*,

BACKGROUND: Children with T-lineage acute lymphoblastic leukemia ALL (T-ALL) historically have had inferior outcomes compared with the children with precursor-B ALL (B-ALL). After 1995,

the Children's Cancer Group (CCG) treated patients with B- and T-ALL according to the National Cancer Institute (NCI) risk criteria, basing risk stratification on age and white blood cell (WBC) count regardless of immunophenotype. The Pediatric Oncology Group (POG) treated all the patients with T-ALL on separate, generally more intensive protocols than those used to treat the patients with B-ALL. PROCEDURE: We compared the outcomes of children with T-ALL and NCI standard-risk (SR) criteria treated on CCG and POG trials between 1996 and 2005. CCG SR-ALL 1952 and 1991 enrolled 80 and 86 patients with T-ALL, respectively, utilizing a reduced intensity Berlin-Frankfurt-Munster backbone. Treatment was intensified for slow early responders and only patients with overt central nervous system leukemia received cranial irradiation. Eighty-four patients with T-ALL and SR features were enrolled on POG 9404 comprising more intensive therapy with all patients receiving cranial irradiation. RESULTS: The 7-year event-free survival (EFS) for patients with SR T-ALL on CCG 1952, CCG 1991, and POG 9404 were 74.1 +/- 5.8%, 81.8 +/- 5.3%, and 84.2 +/- 4.3%, respectively (P = 0.18). Overall 7-year survivals were 86.1 +/- 4.6%, 88.3 +/- 4.4%, 89.1 +/- 3.6%, respectively (P = 0.84). CONCLUSIONS: Comparable high rates of EFS and long-term survival were achieved with all three regimens, with the CCG regimens utilizing a less intensive chemotherapy backbone without prophylactic cranial irradiation for patients with SR T-ALL.

Maxson, J. E., Luty, S. B., MacManiman, J. D., Paik, J. C., Gotlib, J., Greenberg, P., et al. (2015). The colony stimulating factor 3 receptor T640N mutation is oncogenic, sensitive to JAK inhibition, and mimics T618I. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*,

PURPOSE: 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: Due to its similarities to CSF3R T618I, the T640N mutation likely has diagnostic and therapeutic relevance in CNL/aCML.

McCarthy, M. P. (2015). Advance care planning: The dietitian's role (part 2). *Journal of Renal Nutrition : The Official Journal of the Council on Renal Nutrition of the National Kidney Foundation*, 25(6), e49-50.

McCleery, E. J., Patchanee, P., Pongsopawijit, P., Chailangkarn, S., Tiwananthagorn, S., Jongchansittoe, P., et al. (2015). Taeniasis among refugees living on Thailand–Myanmar border, 2012. *Emerging Infectious Diseases*, 21(10), 1824-1826.

We tested refugee camp residents on the Thailand–Myanmar border for *Taenia solium* infection. Taeniasis prevalence was consistent with that for other disease-endemic regions, but seropositivity indicating *T. solium* taeniasis was rare. Seropositivity indicating cysticercosis was 5.5% in humans and 3.2% in pigs. Corraling pigs and providing latrines may control transmission of these tapeworms within this camp. © 2015, Centers for Disease Control and Prevention (CDC). All rights reserved.

McLafferty, R. B. (2015). If you build it...why won't they come? *Journal of Vascular Surgery*, 62(5), 1348-1352.

Meagher, R. K., Daros, R. R., Costa, J. H. C., Von Keyserlingk, M. A. G., Hötzel, M. J., Weary, D. M., et al. (2015). Effects of degree and timing of social housing on reversal learning and response to

novel objects in dairy calves. *Plos One*, 10(8)

Rodents and primates deprived of early social contact exhibit deficits in learning and behavioural flexibility. They often also exhibit apparent signs of elevated anxiety, although the relationship between these effects has not been studied. To investigate whether dairy calves are similarly affected, we first compared calves housed in standard individual pens ( $n = 7$ ) to those housed in a dynamic group with access to their mothers ( $n = 8$ ). All calves learned to approach the correct stimulus in a visual discrimination task. Only one individually housed calf was able to re-learn the task when the stimuli were reversed, compared to all but one calf from the group. A second experiment investigated whether this effect might be explained by anxiety in individually housed animals interfering with their learning, and tested varying degrees of social contact in addition to the complex group: pair housing beginning early (approximately 6 days old) and late (6 weeks old). Again, fewer individually reared calves learned the reversal task (2 of 10 or 20%) compared to early paired and grouped calves (16 of 21 or 76% of calves). Late paired calves had intermediate success. Individually housed calves were slower to touch novel objects, but the magnitude of the fear response did not correlate with reversal performance. We conclude that individually housed calves have learning deficits, but these deficits were not likely associated with increased anxiety. © 2015 Meagher 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.

Mease, P., Deodhar, A., Fleischmann, R., Wollenhaupt, J., Gladman, D., Leszczynski, P., et al. (2015). Effect of certolizumab pegol over 96 weeks in patients with psoriatic arthritis with and without prior antitumour necrosis factor exposure. *RMD Open*, 1(1), e000119-2015-000119. eCollection 2015.

OBJECTIVE: Previous reports of RAPID-PsA (NCT01087788) demonstrated efficacy and safety of certolizumab pegol (CZP) over 24 weeks in patients with psoriatic arthritis (PsA), including patients with prior antitumour necrosis factor (TNF) therapy. We report efficacy and safety data from a 96-week data cut of RAPID-PsA. METHODS: RAPID-PsA was placebo-controlled to week 24, dose-blind to week 48 and open-label to week 216. We present efficacy data including American College of Rheumatology (ACR)/Psoriasis Area and Severity Index (PASI) responses,

HAQ-DI, pain, minimal disease activity (MDA), modified total Sharp score (mTSS) and ACR responses in patients with/without prior anti-TNF exposure, in addition to safety data. RESULTS: Of 409 patients randomised, 273 received CZP from week 0. 54 (19.8%) CZP patients had prior anti-TNF exposure. Of patients randomised to CZP, 91% completed week 24, 87% week 48 and 80% week 96. ACR responses were maintained to week 96: 60% of patients achieved ACR20 at week 24, and 64% at week 96. Improvements were observed with both CZP dose regimens. ACR20 responses were similar in patients with (week 24: 59%; week 96: 63%) and without (week 24: 60%; week 96: 64%) prior anti-TNF exposure. Placebo patients switching to CZP displayed rapid clinical improvements, maintained to week 96. In patients with  $\geq 3\%$  baseline skin involvement (60.8% week 0 CZP patients), PASI responses were maintained to week 96. No progression of structural damage was observed over the 96-week period. In the Safety Set (n=393), adverse events occurred in 345 patients (87.8%) and serious adverse events in 67 (17.0%), including 6 fatal events. CONCLUSIONS: CZP efficacy was maintained to week 96 with both dose regimens and in patients with/without prior anti-TNF exposure. The safety profile was in line with that previously reported from RAPID-PsA, with no new safety signals observed with increased exposure. TRIAL REGISTRATION NUMBER: NCT01087788.

Meyer, C., Haberthur, K., Asquith, M., & Messaoudi, I. (2015). Flow cytometry-based methods to characterize immune senescence in nonhuman primates. *Methods in Molecular Biology (Clifton, N.J.)*, 1343, 65-80.

Flow cytometry is an invaluable technique that can be used to phenotypically and functionally characterize immune cell populations ex vivo. This technology has greatly advanced our ability to gain critical insight into age-related changes in immune function, commonly known as immune senescence. Rodents have been traditionally used to investigate the molecular mechanisms of immune senescence because they offer the distinct advantages of an extensive set of reagents, the presence of genetically modified strains, and a short lifespan that allows for longevity studies of short duration. More recently, nonhuman primates (NHPs), and specifically rhesus macaques, have emerged as a leading translational model to study various aspects of human aging. In contrast to rodents, they share significant genetic homology as well as physiological and behavioral characteristics with humans. Furthermore, rhesus macaques are a long-lived outbred

species, which makes them an ideal translational model. Therefore, NHPs offer a unique opportunity to carry out mechanistic studies under controlled laboratory conditions (e.g., photoperiod, temperature, diet, and medications) in a species that closely mimics human biology. Moreover similar techniques (e.g., activity recording and MRI) can be used to measure physiological parameters in NHPs, making direct comparisons between NHP and human data sets possible. In addition, the outbred genetics of NHPs enables rigorous validation of research findings that goes beyond proof of principle. Finally, self-selection bias that is often unavoidable in human clinical trials can be completely eliminated with NHP studies. Here we describe flow cytometry-based methods to phenotypically and functionally characterize innate immune cells as well as T and B lymphocyte subsets from isolated peripheral blood mononuclear cells (PBMC) in rhesus macaques.

Meyer, M. R., Shaffer, B. L., Doss, A. E., Cahill, A. G., Snowden, J. M., & Caughey, A. B. (2015).

Prospective risk of fetal death with gastroschisis. *Journal of Maternal-Fetal and Neonatal Medicine*, 28(17), 2126-2129.

Objective: To evaluate the ongoing risk of intrauterine fetal demise (IUFD) in fetuses with gastroschisis compared to non-anomalous fetuses. Methods: This was a retrospective cohort study of all births in the United States in 2005-2006, as recorded in the National Center for Health Statistics natality database. Risk of IUFD in fetuses with gastroschisis was compared to non-anomalous fetuses, utilizing total at-risk fetuses as the denominator. Results: Risk of IUFD in fetuses with gastroschisis was 4.5%, compared to 0.6% in non-anomalous fetuses ( $p < 0.001$ ). When controlling for gestational age and other confounders, the adjusted odds ratio for IUFD in fetuses with gastroschisis was 7.06 (95% CI: 3.33-14.96). After 32 weeks, risk of IUFD/ongoing pregnancy was greater at each week of gestation in fetuses with gastroschisis. Conclusions: Risk of IUFD for fetuses with gastroschisis is greater than in non-anomalous fetuses. This risk increases significantly after 32 weeks gestation. Demographic variables are associated with higher rates of gastroschisis and ultimately IUFD. These data may be useful in consideration of timing of delivery. © 2014 © 2014 Informa UK Ltd.

Mokhtarani, M., Diaz, G. A., Lichter-Konecki, U., Berry, S. A., Bartley, J., McCandless, S. E., et al.

(2015). Urinary phenylacetylglutamine (U-PAGN) concentration as biomarker for adherence in patients with urea cycle disorders (UCD) treated with glycerol phenylbutyrate. *Molecular Genetics and Metabolism Reports*, 5, 12-14.

Urinary phenylacetylglutamine (U-PAGN) concentrations in spot urine samples were analyzed as a dosing biomarker during glycerol phenylbutyrate (GPB) dosing in 68 healthy adults and 66 adult and pediatric patients with urea cycle disorders who participated in GPB clinical trials. Age- and body surface area (BSA)-specific 25th percentile cutoff points for spot U-PAGN concentrations ( 2 years with BSA  $\leq$  1.3 m<sup>2</sup> and 2 years of age with BSA > 1.3 m<sup>2</sup>) were determined as an approach to identify patients for whom increased dosing and/or adherence to prescribed dosing should be assessed. © 2015 Published by Elsevier Inc.

Møller, C. L., Pedersen, S. B., Richelsen, B., Conde-Frieboes, K. W., Raun, K., Grove, K. L., et al.

(2015). Melanocortin agonists stimulate lipolysis in human adipose tissue explants but not in adipocytes obesity. *BMC Research Notes*, 8(1)

Background: The central melanocortin system is broadly involved in the regulation of mammalian nutrient utilization. However, the function of melanocortin receptors (MCRs) expressed directly in peripheral metabolic tissues is still unclear. The objective of this study was to investigate the lipolytic capacity of MC1-5R in differentiated adipocytes versus intact white adipose tissue.

Results: Non-selective MCR agonist  $\alpha$ -MSH, MC5R-selective agonist PG-901 and MC4R-selective agonist LY2112688 significantly stimulated lipolysis in intact white adipose tissue, whereas stimulation of MCRs in differentiated adipocytes failed to do so. The lipolytic response of MC5R was decreased in intact human white adipose tissue when co-treating with  $\beta$ -adrenergic antagonist propranolol, suggesting that the effect may be dependent on neuronal innervation via noradrenalin release. Conclusion: When developing an anti-obesity therapeutic drug with selective MC4R/MC5R properties, effects on lipolysis in white adipose tissue may be physiologically relevant. © 2015 Møller et al.

Molto, A., Etcheto, A., van der Heijde, D., Landewe, R., van den Bosch, F., Bautista Molano, W., et al.

(2015). Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: Results

of the international cross-sectional ASAS-COMOSPA study. *Annals of the Rheumatic Diseases*,

**BACKGROUND:** Increased risk of some comorbidities has been reported in spondyloarthritis (SpA). Recommendations for detection/management of some of these comorbidities have been proposed, and it is known that a gap exists between these and their implementation in practice.

**OBJECTIVE:** To evaluate (1) the prevalence of comorbidities and risk factors in different countries worldwide, (2) the gap between available recommendations and daily practice for management of these comorbidities and (3) the prevalence of previously unknown risk factors detected as a

result of the present initiative. **METHODS:** Cross-sectional international study with 22 participating countries (from four continents), including 3984 patients with SpA according to the

rheumatologist. **STATISTICAL ANALYSIS:** The prevalence of comorbidities (cardiovascular, infection, cancer, osteoporosis and gastrointestinal) and risk factors; percentage of patients optimally monitored for comorbidities according to available recommendations and percentage of

patients for whom a risk factor was detected due to this study. **RESULTS:** The most frequent comorbidities were osteoporosis (13%) and gastroduodenal ulcer (11%). The most frequent risk factors were hypertension (34%), smoking (29%) and hypercholesterolaemia (27%). Substantial intercountry variability was observed for screening of comorbidities (eg, for LDL cholesterol

measurement: from 8% (Taiwan) to 98% (Germany)). Systematic evaluation (eg, blood pressure (BP), cholesterol) during this study unveiled previously unknown risk factors (eg, elevated BP (14%)), emphasising the suboptimal monitoring of comorbidities. **CONCLUSIONS:** A high

prevalence of comorbidities in SpA has been shown. Rigorous application of systematic evaluation of comorbidities may permit earlier detection, which may ultimately result in an improved outcome of patients with SpA.

Monsell, S. E., Dodge, H. H., Zhou, X. H., Bu, Y., Besser, L. M., Mock, C., et al. (2015). Results from the NACC uniform data set neuropsychological battery crosswalk study. *Alzheimer Disease and Associated Disorders*,

**INTRODUCTION:** Four new nonproprietary tests were recommended for use in the National Alzheimer's Coordinating Center's Uniform Data Set Neuropsychological Battery. These tests are similar to previous tests but also allow for continuity of longitudinal data collection and wide dissemination among research collaborators. **METHODS:** A Crosswalk Study was conducted in

early 2014 to assess the correlation between each set of new and previous tests. Tests with good correlation were equated using equipercntile equating. The resulting conversion tables allow scores on the new tests to be converted to equivalent scores on the previous tests. RESULTS: All pairs of tests had good correlation ( $\rho=0.68$  to  $0.78$ ). Learning effects were detected for Logical Memory only. Confidence intervals were narrow at each point estimate, and prediction accuracy was high. DISCUSSION: The recommended new tests are well correlated with the previous tests. The equipercntile equating method produced conversion tables that provide a useful reference for clinicians and researchers.

Murphy-Baum, B. L., & Taylor, W. R. (2015). The synaptic and morphological basis of orientation selectivity in a polyaxonal amacrine cell of the rabbit retina. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *35*(39), 13336-13350.

Much of the computational power of the retina derives from the activity of amacrine cells, a large and diverse group of GABAergic and glycinergic inhibitory interneurons. Here, we identify an ON-type orientation-selective, wide-field, polyaxonal amacrine cell (PAC) in the rabbit retina and demonstrate how its orientation selectivity arises from the structure of the dendritic arbor and the pattern of excitatory and inhibitory inputs. Excitation from ON bipolar cells and inhibition arising from the OFF pathway converge to generate a quasi-linear integration of visual signals in the receptive field center. This serves to suppress responses to high spatial frequencies, thereby improving sensitivity to larger objects and enhancing orientation selectivity. Inhibition also regulates the magnitude and time course of excitatory inputs to this PAC through serial inhibitory connections onto the presynaptic terminals of ON bipolar cells. This presynaptic inhibition is driven by graded potentials within local microcircuits, similar in extent to the size of single bipolar cell receptive fields. Additional presynaptic inhibition is generated by spiking amacrine cells on a larger spatial scale covering several hundred microns. The orientation selectivity of this PAC may be a substrate for the inhibition that mediates orientation selectivity in some types of ganglion cells. SIGNIFICANCE STATEMENT: The retina comprises numerous excitatory and inhibitory circuits that encode specific features in the visual scene, such as orientation, contrast, or motion. Here, we identify a wide-field inhibitory neuron that responds to visual stimuli of a particular orientation, a feature selectivity that is primarily due to the elongated shape of the dendritic

arbor. Integration of convergent excitatory and inhibitory inputs from the ON and OFF visual pathways suppress responses to small objects and fine textures, thus enhancing selectivity for larger objects. Feedback inhibition regulates the strength and speed of excitation on both local and wide-field spatial scales. This study demonstrates how different synaptic inputs are regulated to tune a neuron to respond to specific features in the visual scene.

Nagarajan, S., Choi, M. J., Cho, Y. S., Min, S. -, Keum, G., Kim, S. J., et al. (2015). Tubulin inhibitor identification by bioactive conformation alignment pharmacophore-guided virtual screening. *Chemical Biology and Drug Design*, 86(5), 998-1016.

Microtubules are important cellular component that are critical for proper cellular function. Microtubules are synthesized by polymerization of  $\alpha\beta$  tubulin heterodimers called protofilaments. Microtubule dynamics facilitate proper cell division during mitosis. Disruption of microtubule dynamics by small-molecule agents inhibits mitosis, resulting in apoptotic cell death and preventing cell cycle progression. To identify a novel small molecule that binds the  $\alpha\beta$  tubulin interface to affect microtubule dynamics, we developed a bioactive conformation alignment pharmacophore (BCAP) model to screen tubulin inhibitors from a huge database. The application of BCAP model generated based on the known  $\alpha\beta$ -tubulin interface binders enabled us to identify several small-molecules that cause apoptosis in human promyelocytic leukemia (HL-60) cells. Virtual screening combined with an in vitro assay yielded 15 cytotoxic molecules. In particular, ethyl 2-(4-(5-methyl-3-nitro-1H-pyrazol-1-yl)butanamido)-4-phenylthiophene-3-carboxylate (H05) inhibited tubulin polymerization with an IC<sub>50</sub> of 17.6  $\mu$ m concentration. The virtual screening results suggest that the application of an unbiased BCAP pharmacophore greatly eliminates unlikely compounds from a huge database and maximizes screening success. From the limited compounds tested in the tubulin polymerization inhibitor (TPI) assay, compound H05 was discovered as a tubulin inhibitor. This compound requires further structure activity optimization to identify additional potent inhibitors from the same class of molecules. Bioactive conformation alignment pharmacophore (BCAP) model generated based on protein ligand interaction represented at the  $\alpha\beta$  tubulin heterodimers interface in the left panel. The final hit molecule H05 identified from the BCAP and docking screening shown in the right panel. © 2015 John Wiley & Sons A/S.

Narayanan, K., Uy-Evanado, A., Teodorescu, C., Reinier, K., Nichols, G. A., Gunson, K., et al. (2015).

Mitral valve prolapse and sudden cardiac arrest in the community. *Heart Rhythm : The Official Journal of the Heart Rhythm Society*,

BACKGROUND: Mitral valve prolapse (MVP) is relatively common in the general population with recently reported prevalence of 1% and familial clustering (Framingham Heart Study). However, its association with ventricular arrhythmias and sudden cardiac arrest (SCA) remains

controversial. OBJECTIVES: The purpose of this study was to ascertain the frequency of MVP in SCA cases in the community and characterize the clinical profile of SCA cases with MVP.

METHODS: SCA cases were prospectively identified in the population-based Oregon Sudden Unexpected Death Study (population ~1 million). The presence of MVP was identified from echocardiograms recorded prior but unrelated to the SCA event. The detailed clinical profile of SCA cases with MVP was compared with that of SCA cases without MVP to identify potential differences. RESULTS: A total of 729 SCA cases were evaluated over a 12-year period (mean age 69.5 +/- 14.8 years; 64.6% men). MVP was seen in 17 cases (2.3%) prearrest (95% confidence interval 1.2%-3.4%). Mitral regurgitation was present in 14 SCA cases with MVP (82.3%) and was moderate or severe in 10 (58.8%). Compared with SCA cases without MVP, SCA cases with MVP were younger (mean age 60.9 +/- 16.4 years vs 69.7 +/- 14.7 years; P = .02), with fewer risk factors (diabetes 5.9% vs 46.4%; P = .001; hypertension 41.2% vs 78.9%; P = .001) or known coronary disease (29.4% vs 65.6%; P < .001). CONCLUSION: MVP was observed in a small proportion (2.3%) of SCA cases in the general population, suggesting a low risk overall. Since SCA cases with MVP were characterized by younger age and relatively low cardiovascular comorbidity, a focus on imaging for valve structure/insufficiency as well as genetics could aid future risk stratification approaches.

Nasir, K., Bittencourt, M. S., Blaha, M. J., Blankstein, R., Agatston, A. S., Rivera, J. J., et al. (2015).

Implications of coronary artery calcium testing among statin candidates according to American college of Cardiology/American heart association cholesterol management guidelines MESA (multi-ethnic study of atherosclerosis). *Journal of the American College of Cardiology*, 66(15), 1657-1668.

Background The American College of Cardiology (ACC)/American Heart Association (AHA)

cholesterol management guidelines have significantly broadened the scope of candidates eligible for statin therapy. Objectives This study evaluated the implications of the absence of coronary artery calcium (CAC) in reclassifying patients from a risk stratum in which statins are recommended to one in which they are not. Methods MESA (Multi-Ethnic Study of Atherosclerosis) is a longitudinal study of 6,814 men and women 45 to 84 years of age without clinical atherosclerotic cardiovascular disease (ASCVD) risk at enrollment. We excluded 1,100 participants (16%) on lipid-lowering medication, 87 (1.3%) without low-density lipoprotein levels, 26 (0.4%) with missing risk factors for calculation of 10-year risk of ASCVD, 633 (9%) >75 years of age, and 209 (3%) with low-density lipoprotein <70 mg/dl from the analysis. Results The study population consisted of 4,758 participants (age 59 ± 9 years; 47% males). A total of 247 (5.2%) ASCVD and 155 (3.3%) hard coronary heart disease events occurred over a median (interquartile range) follow-up of 10.3 (9.7 to 10.8) years. The new ACC/AHA guidelines recommended 2,377 (50%) MESA participants for moderate- to high-intensity statins; the majority (77%) was eligible because of a 10-year estimated ASCVD risk ≥7.5%. Of those recommended statins, 41% had CAC = 0 and had 5.2 ASCVD events/1,000 person-years. Among 589 participants (12%) considered for moderate-intensity statin, 338 (57%) had a CAC = 0, with an ASCVD event rate of 1.5 per 1,000 person-years. Of participants eligible (recommended or considered) for statins, 44% (1,316 of 2,966) had CAC = 0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1,000 person-years. Conclusions Significant ASCVD risk heterogeneity exists among those eligible for statins according to the new guidelines. The absence of CAC reclassifies approximately one-half of candidates as not eligible for statin therapy. © 2015 American College of Cardiology Foundation.

Nelson, H. D. (2015). Mammography screening and overdiagnosis. *JAMA Oncology*, , 1-2.

Nemoto, O., Furue, M., Nakagawa, H., Shiramoto, M., Hanada, R., Matsuki, S., et al. (2015). The first trial of CIM331, a humanized anti-human IL-31 receptor A antibody, for healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomised, double-blind, placebo-controlled study. *The British Journal of Dermatology*, BACKGROUND: Interleukin-31 (IL-31) is considered as a responsible cytokine for the

development of pruritus in humans. At present, no available evidence has been reported on the safety and efficacy of blocking the IL-31 signal in humans for the amelioration of pruritus in atopic dermatitis (AD). CIM331 is a humanized anti-human IL-31 receptor A monoclonal antibody, which binds to IL-31 receptor A to inhibit subsequent IL-31 signalling. OBJECTIVES: To assess the tolerability, safety, pharmacokinetics and preliminary efficacy of CIM331 in healthy Japanese and Caucasian volunteers and Japanese patients with AD. METHODS: In this randomised, double-blind, placebo-controlled phase I/Ib study, CIM331 was administered in a single dose subcutaneously. The primary outcomes were safety and tolerability and the exploratory analysis was efficacy. RESULTS: No deaths, serious adverse events (AEs) or discontinuations due to AEs were reported in any study part. No dose-dependent increase in the incidence of AEs occurred in any study part. In healthy volunteers, all AEs occurred once in the placebo groups, and increased creatine phosphokinase was more common in the CIM331 groups. In AD patients, CIM331 reduced pruritus visual analogue scale score to about -50% at Week 4 with CIM331, compared with -19.7% with placebo. CIM331 increased sleep efficiency and decreased the use of hydrocortisone butyrate. CONCLUSIONS: Single subcutaneous administration of CIM331 was well tolerated in healthy volunteers and patients with AD. It decreased pruritus, sleep disturbance and topical use of hydrocortisone. CIM331 may become a novel therapeutic option for AD through inhibiting IL-31. This article is protected by copyright. All rights reserved.

Newgard, C. D., Holmes, J. F., Haukoos, J. S., Bulger, E. M., Staudenmayer, K., Wittwer, L., et al.

(2015). Improving early identification of the high-risk elderly trauma patient by emergency medical services. *Injury*,

STUDY OBJECTIVE: We sought to (1) define the high-risk elderly trauma patient based on prognostic differences associated with different injury patterns and (2) derive alternative field trauma triage guidelines that mesh with national field triage guidelines to improve identification of high-risk elderly patients. METHODS: This was a retrospective cohort study of injured adults  $\geq 65$  years transported by 94 EMS agencies to 122 hospitals in 7 regions from 1/1/2006 through 12/31/2008. We tracked current field triage practices by EMS, patient demographics, out-of-hospital physiology, procedures and mechanism of injury. Outcomes included Injury

Severity Score  $\geq 16$  and specific anatomic patterns of serious injury using abbreviated injury scale score  $\geq 3$  and surgical interventions. In-hospital mortality was used as a measure of prognosis for different injury patterns. RESULTS: 33,298 injured elderly patients were transported by EMS, including 4.5% with ISS  $\geq 16$ , 4.8% with serious brain injury, 3.4% with serious chest injury, 1.6% with serious abdominal-pelvic injury and 29.2% with serious extremity injury. In-hospital mortality ranged from 18.7% (95% CI 16.7-20.7) for ISS  $\geq 16$  to 2.9% (95% CI 2.6-3.3) for serious extremity injury. The alternative triage guidelines (any positive criterion from the current guidelines, GCS  $\geq 16$ : sensitivity (92.1% [95% CI 89.6-94.1%] vs. 75.9% [95% CI 72.3-79.2%]), specificity (41.5% [95% CI 40.6-42.4%] vs. 77.8% [95% CI 77.1-78.5%])). Sensitivity decreased for individual injury patterns, but was higher than current triage practices. CONCLUSIONS: High-risk elderly trauma patients can be defined by ISS  $\geq 16$  or specific non-extremity injury patterns. The field triage guidelines could be improved to better identify high-risk elderly trauma patients by EMS, with a reduction in triage specificity.

Nguyen, K. P., McGilvray, K. C., Puttlitz, C. M., Mukhopadhyay, S., Chabasse, C., & Sarkar, R. (2015).

Matrix metalloproteinase 9 (MMP-9) regulates vein wall biomechanics in murine thrombus resolution. *PLoS One*, 10(9), e0139145.

OBJECTIVE: Deep venous thrombosis is a common vascular problem with long-term complications including post-thrombotic syndrome. Post-thrombotic syndrome consists of leg pain, swelling and ulceration that is related to incomplete or maladaptive resolution of the venous thrombus as well as loss of compliance of the vein wall. We examine the role of metalloproteinase-9 (MMP-9), a gene important in extracellular remodeling in other vascular diseases, in mediating thrombus resolution and biomechanical changes of the vein wall.

METHODS AND RESULTS: The effects of targeted deletion of MMP-9 were studied in an in vivo murine model of thrombus resolution using the FVB strain of mice. MMP-9 expression and activity significantly increased on day 3 after DVT. The lack of MMP-9 impaired thrombus resolution by 27% and this phenotype was rescued by the transplantation of wildtype bone marrow cells. Using novel biomechanical techniques, we demonstrated that the lack of MMP-9 significantly decreased thrombus-induced loss of vein wall compliance. Biomechanical analysis of the contribution of individual structural components showed that MMP-9 affected the elasticity of the extracellular

matrix and collagen-elastin fibers. Biochemical and histological analyses correlated with these biomechanical effects as thrombi of mice lacking MMP-9 had significantly fewer macrophages and collagen as compared to those of wildtype mice. CONCLUSIONS: MMP-9 mediates thrombus-induced loss of vein wall compliance by increasing stiffness of the extracellular matrix and collagen-elastin fibers during thrombus resolution. MMP-9 also mediates macrophage and collagen content of the resolving thrombus and bone-marrow derived MMP-9 plays a role in resolution of thrombus mass. These disparate effects of MMP-9 on various aspects of thrombus illustrate the complexity of individual protease function on biomechanical and morphometric aspects of thrombus resolution.

Nickel, R. E., & Huang-Storms, L. (2015). Early identification of young children with autism spectrum disorder. *Indian Journal of Pediatrics,*

Early identification and treatment of children with autism and other developmental disorders is an international priority. Currently there is great interest in lowering the age of identification.

Attention has been focused on public awareness campaigns and the regular use of developmental screening tests by health care providers, health workers and others. In this article the authors discuss the rationale for the use of autism specific screening tests, review the characteristics of selected tools, and make recommendations for the diagnostic evaluation of young children for autism spectrum disorder in an international context.

Nicolaidis, C., Raymaker, D., Katz, M., Oswald, M., Goe, R., Leotti, S., et al. (2015). Community-based participatory research to adapt health measures for use by people with developmental disabilities. *Progress in Community Health Partnerships: Research, Education, and Action, 9(2),* 141-143.

Nicolson, T. (2015). It takes two. *Elife, 4,* 10.7554/eLife.11399.

Two forms of an unconventional myosin motor protein have separate functions in the growth and maintenance of hair bundles in auditory hair cells.

Nowomiejska, K., Brzozowska, A., Koss, M. J., Weleber, R. G., Schiefer, U., Rejdak, K., et al. (2015). Quantification of the visual field loss in retinitis pigmentosa using semi-automated kinetic

perimetry. *Current Eye Research*, , 1-6.

**PURPOSE:** To assess quantitatively the natural course of the visual field (VF) loss in patients with retinitis pigmentosa (RP) during 2-year period of observation. **METHODS:** VFs were obtained by semi-automated kinetic perimetry (SKP) during four examinations of 16 patients suffering from RP. Three stimulus conditions (V4e, III4e and I4e) with a constant stimulus angular velocity of 3 degrees /s were used to assess the hill of vision in both eyes of each patient. The area of each isopter was measured in square degrees and corrected for the individual reaction time (RT).

**RESULTS:** There were four patients with mild restriction of VF, six with ring scotomas and six with advanced concentric constrictions of VF. Only I4e isopter area decreased significantly from the first to the last session ( $p = 0.006$ ), the difference was 154 deg<sup>2</sup> being 13% of initial isopter area. The difference was not significant for V4e and III4e isopters. RT values did not differ significantly between four sessions. **CONCLUSIONS:** Only I4e isopter's area was decreased significantly during two years of observation. SKP provides a method of assessment of progression of the VF loss in patients suffering from RP by measurement of the isopters' area over time.

Okoye, A. A., Rohankhedkar, M., Konfe, A. L., Abana, C. O., Reyes, M. D., Clock, J. A., et al. (2015). Effect of IL-7 therapy on naive and memory T cell homeostasis in aged rhesus macaques. *Journal of Immunology (Baltimore, Md.: 1950)*, 195(9), 4292-4305.

Aging is associated with gradual deterioration of adaptive immune function, a hallmark of which is the profound loss of naive T cells (TN) associated with decline in thymic output and export of new cells into the peripheral T cell pool. Because the lymphotropic cytokine IL-7 plays crucial roles in both development of TN in the thymus and TN homeostasis in the periphery, we sought to determine the extent to which therapeutic administration of IL-7 could reverse TN deficiency in aging rhesus macaques (RM), either by enhancement of the demonstrably reduced thymopoiesis or by peripheral TN expansion. Our results indicate that treatment of both adult (8-15 y) and old (>20 y) RM with recombinant simian IL-7 (rsIL-7) results in only transient increases in peripheral CD4(+) and CD8(+) TN numbers with no long-term benefit, even with repeated therapy. This transient effect was due to peripheral TN expansion and not enhanced thymic function, and appeared to be limited by induction of IL-7 nonresponsiveness. However, rsIL-7 therapy had a

more promising effect on the central memory T cell (TCM) population (both CD4(+) and CD8(+)) in adult and old RM, doubling the numbers of these cells in circulation and maintaining this larger population long term. IL-7 therapy did not reduce TCR diversity of the memory T cell compartment, suggesting that rsIL-7-induced expansion was symmetrical. Thus, although rsIL-7 failed to counter age-associated TN loss, the ability of this therapy to expand clonotypically diverse CD4(+) and CD8(+) TCM populations might potentially improve adaptive immune responsiveness in the elderly.

Ozburn, A. R., Janowsky, A. J., & Crabbe, J. C. (2015). Commonalities and distinctions among mechanisms of addiction to alcohol and other drugs. *Alcoholism, Clinical and Experimental Research*, 39(10), 1863-1877.

BACKGROUND: Alcohol abuse is comorbid with abuse of many other drugs, some with similar pharmacology and others quite different. This leads to the hypothesis of an underlying, unitary dysfunctional neurobiological basis for substance abuse risk and consequences. METHODS: In this review, we discuss commonalities and distinctions of addiction to alcohol and other drugs. We focus on recent advances in preclinical studies using rodent models of drug self-administration. RESULTS: While there are specific behavioral and molecular manifestations common to alcohol, psychostimulant, opioid, and nicotine dependence, attempts to propose a unifying theory of the addictions inevitably face details where distinctions are found among classes of drugs. CONCLUSIONS: For alcohol, versus other drugs of abuse, we discuss and compare advances in: (i) neurocircuitry important for the different stages of drug dependence; (ii) transcriptomics and genetical genomics; and (iii) enduring effects, noting in particular the contributions of behavioral genetics and animal models.

Palejwala, N. V., Jia, Y., Gao, S. S., Liu, L., Flaxel, C. J., Hwang, T. S., et al. (2015). Detection of nonexudative choroidal neovascularization in age-related macular degeneration with optical coherence tomography angiography. *Retina*,

PURPOSE:: To evaluate eyes with age-related macular degeneration and high-risk characteristics for choroidal neovascularization (CNV) with optical coherence tomographic (OCT) angiography to determine whether earlier detection of CNV is possible. METHODS:: Eyes with drusen,

pigmentary changes, and with CNV in the fellow eye were scanned with a 70-kHz spectral domain OCT system (Optovue RTVue-XR Avanti). The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm was used to distinguish blood flow from static tissue. Two masked graders reviewed scans for CNV, defined as flow in the outer retinal/sub-RPE slab. Choroidal neovascularization flow area repeatability and between-grader reproducibility were calculated. RESULTS:: Of 32 eyes, 2 (6%) were found to have Type 1 CNV with OCT angiography. The lesions were not associated with leakage on fluorescein angiography or fluid on OCT. One case was followed for 8 months without treatment, and the CNV flow area enlarged slightly without fluid buildup on OCT or vision loss. Between-grader reproducibility of the CNV flow area was 9.4% (coefficient of variation) and within-visit repeatability was 5.2% (pooled coefficient of variation). CONCLUSION:: Optical coherence tomographic angiography can detect the presence of nonexudative CNV, lesions difficult to identify with fluorescein angiography and OCT. Further study is needed to understand the significance and natural history of these lesions. © 2015 by Ophthalmic Communications Society, Inc.

Parajuli, S., Lockridge, J. B., Langewisch, E. D., Norman, D. J., & Kujovich, J. L. (2015).

Hypercoagulability in kidney transplant recipients. *Transplantation,*

Thrombosis remains an important complication after kidney transplantation. Outcomes for graft and deep vein thrombosis are not favorable. The majority of early kidney transplant failure in adults is due to allograft thrombosis. Risk stratification, early diagnosis, and appropriate intervention are critical to the management of thrombotic complications of transplant. In patients with end-stage renal disease, the prevalence of acquired risk factors for thrombosis is significantly high. Because of hereditary and acquired risk factors, renal transplant recipients manifest features of a chronic prothrombotic state. Identification of hereditary thrombotic risk factors before transplantation may be a useful tool for selecting appropriate candidates for thrombosis prophylaxis immediately after transplantation. Short-term anticoagulation may be appropriate for all patients after kidney transplantation.

Park, J. H., Kang, Y. J., & Horak, F. B. (2015). What is wrong with balance in parkinson's disease?

*Journal of Movement Disorders,* 8(3), 109-114.

Postural instability and resulting falls are major factors determining quality of life, morbidity, and mortality in individuals with Parkinson's disease (PD). A better understanding of balance impairments would improve management of balance dysfunction and prevent falls in patients with PD. The effects of bradykinesia, rigidity, impaired proprioception, freezing of gait and attention on postural stability in patients with idiopathic PD have been well characterized in laboratory studies. The purpose of this review is to systematically summarize the types of balance impairments contributing to postural instability in people with PD.

Parren, P. W., Burton, D. R., Bradbury, A., Huston, J. S., Carter, P. J., Veldman, T., et al. (2015).

Antibody engineering & therapeutics 2015: The antibody society's annual meeting december 7-10, 2015, san diego, CA. *Mabs*, 7(6), 981-988.

Antibody Engineering & Therapeutics, the annual meeting of The Antibody Society, will be held in San Diego, CA in early December 2015. In this meeting preview, the chairs provide their thoughts on the importance of their session topics, which include antibody effector functions, reproducibility of research and diagnostic antibodies, new developments in antibody-drug conjugates (ADCs), preclinical and clinical ADC data, new technologies and applications for bispecific antibodies, antibody therapeutics for non-cancer and orphan indications, antibodies to harness the cellular immune system, overcoming resistance to clinical immunotherapy, and building comprehensive IGVH-gene repertoires through discovering, confirming and cataloging new germline IGVH genes. The Antibody Society's special session will focus on "Antibodies to watch" in 2016, which are a subset of the nearly 50 antibodies currently in Phase 3 clinical studies. Featuring over 100 speakers in total, the meeting will commence with keynote presentations by Erica Ollmann Saphire (The Scripps Research Institute), Wayne A. Marasco (Dana-Farber Cancer Institute/Harvard Medical School), Joe W. Gray (Oregon Health & Science University), and Anna M. Wu (University of California Los Angeles), and it will conclude with workshops on the promise and challenges of using next-generation sequencing for antibody discovery and engineering from synthetic and in vivo libraries and on computational antibody design.

Patil, D. T., Ma, S., Konishi, M., Carver, P. D., Pukay, M., Beadling, C., et al. (2015). Utility of BRAF V600E mutation-specific immunohistochemistry in detecting BRAF V600E-mutated gastrointestinal stromal tumors. *American Journal of Clinical Pathology*, 144(5), 782-789.

OBJECTIVES: As patients with BRAF V600E mutation respond to BRAF inhibitors, it is important to identify these mutations to stratify patients for the appropriate therapy. In this study, we evaluated the utility of a BRAF V600E allele-specific antibody in gastrointestinal stromal tumors (GISTs). METHODS: BRAF V600E mutation-specific immunohistochemistry (negative, weak, or moderate/strong expression) and BRAF sequencing were performed on 38 consecutive GISTs diagnosed between January 2013 and April 2014. RESULTS: GISTs from a cohort of 25 men and 13 women (mean age, 61 years; range, 39-88 years) were localized to the stomach (18), small bowel (10), colon (three), rectum (two), and pelvis/omentum (five). Strong and diffuse cytoplasmic BRAF expression was noted in two (5%) of 38 cases, while eight (21%) of 38 cases showed weak staining, and 28 (74%) of 38 cases were negative. Both of the strongly positive cases arose in the stomach, occurring in a 42-year-old and a 47-year-old woman, respectively. The lesions measured 0.8 and 1 cm, showed spindle cell morphology, and had no risk of progressive disease by Miettinen criteria. Both cases showed heterozygous BRAF V600E, while no BRAF mutations were detected in cases with weak or negative BRAF expression. CONCLUSIONS: BRAF V600E mutation-specific immunohistochemistry is a highly sensitive and specific method for detecting BRAF-mutated GISTs.

Patil, E., & Jensen, J. T. (2015). Update on permanent contraception options for women. *Current Opinion in Obstetrics & Gynecology*, 27(6), 465-470.

PURPOSE OF REVIEW: Permanent methods are the most commonly used contraceptive options worldwide. Even with the increase in popularity and accessibility of long-acting reversible methods, there remains high demand for permanent options, especially among women in developing countries. RECENT FINDINGS: Traditional methods of permanent contraception, such as postpartum tubal ligation and interval surgical tubal occlusion or electrocautery by mini-laparotomy or laparoscopy are well tolerated and highly effective. Bilateral total salpingectomy for ovarian cancer risk reduction is currently being investigated. Hysteroscopic tubal occlusion reduces or eliminates the need for anesthesia, but requires surgical training and specialized

equipment. Alternative permanent contraception methods are being explored including immediately effective hysteroscopic methods, and nonsurgical permanent contraception methods that have the potential to improve access and reduce cost. SUMMARY: Permanent contraception methods are an important part of the contraceptive methods mix designed to meet the needs of women who have completed desired family size or wish never to become pregnant. Current surgical approaches to permanent contraception are well tolerated and highly effective. The development of a highly effective nonsurgical approach could simplify the provision of permanent contraception.

Paul Chan, R. V., Patel, S. N., Ryan, M. C., Jonas, K. E., Ostmo, S., Port, A. D., et al. (2015). The global education network for retinopathy of prematurity (gen-rop): Development, implementation, and evaluation of a novel tele-education system (an american ophthalmological society thesis). *Transactions of the American Ophthalmological Society*, 113

Purpose: To describe the design, implementation, and evaluation of a tele-education system developed to improve diagnostic competency in retinopathy of prematurity (ROP) by ophthalmology residents. Methods: A secure Web-based tele-education system was developed utilizing a repository of over 2,500 unique image sets of ROP. For each image set used in the system, a reference standard ROP diagnosis was established. Performance by ophthalmology residents (postgraduate years 2 to 4) from the United States and Canada in taking the ROP tele-education program was prospectively evaluated. Residents were presented with image-based clinical cases of ROP during a pretest, posttest, and training chapters. Accuracy and reliability of ROP diagnosis (eg, plus disease, zone, stage, category) were determined using sensitivity, specificity, and the kappa statistic calculations of the results from the pretest and posttest. Results: Fifty-five ophthalmology residents were provided access to the ROP tele-education program. Thirty-one ophthalmology residents completed the program. When all training levels were analyzed together, a statistically significant increase was observed in sensitivity for the diagnosis of plus disease, zone, stage, category, and aggressive posterior ROP ( $P < .05$ ). Statistically significant changes in specificity for identification of stage 2 or worse ( $P = .027$ ) and pre-plus ( $P = .028$ ) were observed. Conclusions: A tele-education system for ROP education is effective in improving diagnostic accuracy of ROP by ophthalmology residents. This system may

have utility in the setting of both healthcare and medical education reform by creating a validated method to certify telemedicine providers and educate the next generation of ophthalmologists. © 2015 by the American Ophthalmological Society.

Pazos, M., Yang, H., Gardiner, S. K., Cepurna, W. O., Johnson, E. C., Morrison, J. C., et al. (2015).

Expansions of the neurovascular scleral canal and contained optic nerve occur early in the hypertonic saline rat experimental glaucoma model. *Experimental Eye Research*,

PURPOSE: To characterize early optic nerve head (ONH) structural change in rat experimental glaucoma (EG). METHODS: Unilateral intraocular pressure (IOP) elevation was induced in Brown Norway rats by hypertonic saline injection into the episcleral veins and animals were sacrificed 4 weeks later by perfusion fixation. Optic nerve cross-sections were graded from 1 (normal) to 5 (extensive injury) by 5 masked observers. ONH's with peripapillary retina and sclera were embedded, serial sectioned, 3-D reconstructed, delineated, and quantified. Overall and animal-specific EG versus Control eye ONH parameter differences were assessed globally and regionally by linear mixed effect models with significance criteria adjusted for multiple comparisons.

RESULTS: Expansions of the optic nerve and surrounding anterior scleral canal opening achieved statistical significance overall ( $p < .0022$ ), and in 7 of 8 EG eyes ( $p < .005$ ). In at least 5 EG eyes, significant expansions ( $p < .005$ ) in Bruch's membrane opening (range 3-10%), the anterior and posterior scleral canal openings (8-21% and 5-21%, respectively), and the optic nerve at the anterior and posterior scleral canal openings (11-30% and 8-41%, respectively) were detected. Optic nerve expansion was greatest within the superior and inferior quadrants. Optic nerve expansion at the posterior scleral canal opening was significantly correlated to optic nerve damage ( $R = 0.768$ ,  $P = .042$ ). CONCLUSION: In the rat ONH, the optic nerve and surrounding Bruch's membrane opening and neurovascular scleral canal expand early in their response to chronic experimental IOP elevation. These findings provide phenotypic landmarks and imaging targets for detecting the development of experimental glaucomatous optic neuropathy in the rat eye.

Pechauer, A. D., Huang, D., & Jia, Y. (2015). Detecting blood flow response to stimulation of the human eye. *BioMed Research International*, 2015, 121973.

Retinal blood supply is tightly regulated under a variety of hemodynamic considerations in order to satisfy a high metabolic need and maintain both vessel structure and function. Simulation of the human eye can induce hemodynamics alterations, and attempt to assess the vascular reactivity response has been well documented in the scientific literature. Advancements in noninvasive imaging technologies have led to the characterization of magnitude and time course in retinal blood flow response to stimuli. This allowed for a better understanding of the mechanism in which blood flow is regulated, as well as identifying functional impairments in the diseased eye. Clinically, the ability to detect retinal blood flow reactivity during stimulation of the eye offers potential for the detection, differentiation, and diagnosis of diseases.

Penn, A. A., Gressens, P., Fleiss, B., Back, S. A., & Gallo, V. (2015). Controversies in preterm brain injury. *Neurobiology of Disease*,

In this review, we highlight critical unresolved questions in the etiology and mechanisms causing preterm brain injury. Involvement of neurons, glia, endogenous factors and exogenous exposures is considered. The structural and functional correlates of interrupted development and injury in the premature brain are under active investigation, with the hope that the cellular and molecular mechanisms underlying developmental abnormalities in the human preterm brain can be understood, prevented or repaired.

Perry, C. K., Nagel, C., Ko, L. K., Duggan, C., Linde, S., Rodriguez, E. A., et al. (2015). Active living environment assessments in four rural latino communities. *Preventive Medicine Reports*, 2, 818-823.

Objective: Latinos and rural residents are less active and have a greater prevalence of overweight/obesity compared with their non-Latino white and urban counterparts. The objective of this study was to assess the active living environment in four rural, predominantly Latino communities. Methods: Assessments were taken using the Rural Active Living Assessment (RALA) in four rural predominantly Latino communities in Central Washington from September-November 2013. Street Segment Assessments of town center, thoroughfare, neighborhood and school zones were assessed for features related to walkability. Physical activity amenities, programs and policies in each town were assessed. Scores were generated for amenities, programs and policies.

Data were analyzed with descriptive statistics and logistic regression. Results: A total of 103 segments were assessed. Sidewalks in good condition were present in 32% of segments and shoulders in 44% of segments. Half of street segments were rated as walkable. Parks and playgrounds were available however, half of these were rated in poor condition. All four districts offered after school physical activity programming but only two had a late bus option.

Conclusions: These four rural towns have some policies, programming and infrastructure in place that support active living. The information from the RALA can be used to inform program and policy development to enhance physical activity in these rural communities. © 2015 The Authors.

Petersen, J., Austin, D., Mattek, N., & Kaye, J. (2015). Time out-of-home and cognitive, physical, and emotional wellbeing of older adults: A longitudinal mixed effects model. *PLoS One*, *10*(10), e0139643.

**BACKGROUND:** Time out-of-home has been linked with numerous health outcomes, including cognitive decline, poor physical ability and low emotional state. Comprehensive characterization of this important health metric would potentially enable objective monitoring of key health outcomes. The objective of this study is to determine the relationship between time out-of-home and cognitive status, physical ability and emotional state. **METHODS AND FINDINGS:** Participants included 85 independent older adults, age 65-96 years ( $M = 86.36$ ;  $SD = 6.79$ ) who lived alone, from the Intelligent Systems for Assessing Aging Changes (ISAAC) and the ORCATECH Life Laboratory cohorts. Factors hypothesized to affect time out-of-home were assessed on three different temporal levels: yearly (cognitive status, loneliness, clinical walking speed), weekly (pain and mood) or daily (time out-of-home, in-home walking speed, weather, and season). Subject characteristics including age, race, and gender were assessed at baseline. Total daily time out-of-home in hours was assessed objectively and unobtrusively for up to one year using an in-home activity sensor platform. A longitudinal tobit mixed effects regression model was used to relate daily time out-of-home to cognitive status, physical ability and emotional state. More hours spend outside the home was associated with better cognitive function as assessed using the Clinical Dementia Rating (CDR) Scale, where higher scores indicate lower cognitive function ( $\beta_{CDR} = -1.69$ ,  $p < 0.001$ ). More hours outside the home was also associated with superior physical ability ( $\beta_{Pain} = -0.123$ ,  $p < 0.001$ ) and improved emotional state ( $\beta_{Lonely} = -$

0.046,  $p < 0.001$ ;  $\beta_{\text{Low mood}} = -0.520$ ,  $p < 0.001$ ). Weather, season, and weekday also affected the daily time out-of-home. CONCLUSIONS: These results suggest that objective longitudinal monitoring of time out-of-home may enable unobtrusive assessment of cognitive, physical and emotional state. In addition, these results indicate that the factors affecting out-of-home behavior are complex, with factors such as living environment, weather and season significantly affecting time out-of-home. Studies investigating the relationship between time out-of-home and health outcomes may be optimized by taking into account the environment and life factors presented here.

Petersen, J., Kaye, J., Jacobs, P. G., Quinones, A., Dodge, H., Arnold, A., et al. (2015). Longitudinal relationship between loneliness and social isolation in older adults: Results from the cardiovascular health study. *Journal of Aging and Health*,  
OBJECTIVE: To understand the longitudinal relationship between loneliness and isolation.  
METHOD: Participants included 5,870 adults 65 years and older ( $M = 72.89 \pm 5.59$  years) from the first 5 years of the Cardiovascular Health Study. Loneliness was assessed using a dichotomized loneliness question. Social isolation was assessed using six items from the Lubben Social Network Scale. Yearly life events were included to assess abrupt social network changes. Mixed effects logistic regression was employed to analyze the relationship between isolation and loneliness. RESULTS: Higher levels of social isolation were associated with higher odds of loneliness, as was an increase (from median) in level of social isolation. Life events such as a friend dying were also associated with increased odds of loneliness. DISCUSSION: These results suggest that average level of isolation and increases in the level of isolation are closely tied to loneliness, which has implications for future assessment or monitoring of loneliness in older adult populations.

Pfefferbaum, A., Rohlfing, T., Pohl, K. M., Lane, B., Chu, W., Kwon, D., et al. (2015). Adolescent development of cortical and white matter structure in the NCANDA sample: Role of sex, ethnicity, puberty, and alcohol drinking. *Cerebral Cortex (New York, N.Y.: 1991)*,  
Brain structural development continues throughout adolescence, when experimentation with alcohol is often initiated. To parse contributions from biological and environmental factors on

neurodevelopment, this study used baseline National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) magnetic resonance imaging (MRI) data, acquired in 674 adolescents meeting no/low alcohol or drug use criteria and 134 adolescents exceeding criteria. Spatial integrity of images across the 5 recruitment sites was assured by morphological scaling using Alzheimer's disease neuroimaging initiative phantom-derived volume scalar metrics. Clinical MRI readings identified structural anomalies in 11.4%. Cortical volume and thickness were smaller and white matter volumes were larger in older than in younger adolescents. Effects of sex (male > female) and ethnicity (majority > minority) were significant for volume and surface but minimal for cortical thickness. Adjusting volume and area for supratentorial volume attenuated or removed sex and ethnicity effects. That cortical thickness showed age-related decline and was unrelated to supratentorial volume is consistent with the radial unit hypothesis, suggesting a universal neural development characteristic robust to sex and ethnicity. Comparison of NCANDA with PING data revealed similar but flatter, age-related declines in cortical volumes and thickness. Smaller, thinner frontal, and temporal cortices in the exceeds-criteria than no/low-drinking group suggested untoward effects of excessive alcohol consumption on brain structural development.

Phillips, T. J., & Shabani, S. (2015). An animal model of differential genetic risk for methamphetamine intake. *Frontiers in Neuroscience, 9*, 327.

The question of whether genetic factors contribute to risk for methamphetamine (MA) use and dependence has not been intensively investigated. Compared to human populations, genetic animal models offer the advantages of control over genetic family history and drug exposure. Using selective breeding, we created lines of mice that differ in genetic risk for voluntary MA intake and identified the chromosomal addresses of contributory genes. A quantitative trait locus was identified on chromosome 10 that accounts for more than 50% of the genetic variance in MA intake in the selected mouse lines. In addition, behavioral and physiological screening identified differences corresponding with risk for MA intake that have generated hypotheses that are testable in humans. Heightened sensitivity to aversive and certain physiological effects of MA, such as MA-induced reduction in body temperature, are hallmarks of mice bred for low MA intake. Furthermore, unlike MA-avoiding mice, MA-preferring mice are sensitive to rewarding and

reinforcing MA effects, and to MA-induced increases in brain extracellular dopamine levels. Gene expression analyses implicate the importance of a network enriched in transcription factor genes, some of which regulate the mu opioid receptor gene, *Oprm1*, in risk for MA use. Neuroimmune factors appear to play a role in differential response to MA between the mice bred for high and low intake. In addition, chromosome 10 candidate gene studies provide strong support for a trace amine-associated receptor 1 gene, *Taar1*, polymorphism in risk for MA intake. MA is a trace amine-associated receptor 1 (TAAR1) agonist, and a non-functional *Taar1* allele segregates with high MA consumption. Thus, reduced TAAR1 function has the potential to increase risk for MA use. Overall, existing findings support the MA drinking lines as a powerful model for identifying genetic factors involved in determining risk for harmful MA use. Future directions include the development of a binge model of MA intake, examining the effect of withdrawal from chronic MA on MA intake, and studying potential *Taar1* gene x gene and gene x environment interactions. These and other studies are intended to improve our genetic model with regard to its translational value to human addiction.

Pilkonis, P. A., Yu, L., Dodds, N. E., Johnston, K. L., Lawrence, S. M., Hilton, T. F., et al. (2015). Item banks for substance use from the patient-reported outcomes measurement information system (PROMIS((R))): Severity of use and positive appeal of use. *Drug and Alcohol Dependence*, 156, 184-192.

**BACKGROUND:** Two item banks for substance use were developed as part of the Patient-Reported Outcomes Measurement Information System (PROMIS((R))): severity of substance use and positive appeal of substance use. **METHODS:** Qualitative item analysis (including focus groups, cognitive interviewing, expert review, and item revision) reduced an initial pool of more than 5300 items for substance use to 119 items included in field testing. Items were written in a first-person, past-tense format, with 5 response options reflecting frequency or severity. Both 30-day and 3-month time frames were tested. The calibration sample of 1336 respondents included 875 individuals from the general population (ascertained through an internet panel) and 461 patients from addiction treatment centers participating in the National Drug Abuse Treatment Clinical Trials Network. **RESULTS:** Final banks of 37 and 18 items were calibrated for severity of substance use and positive appeal of substance use, respectively, using the two-parameter

graded response model from item response theory (IRT). Initial calibrations were similar for the 30-day and 3-month time frames, and final calibrations used data combined across the time frames, making the items applicable with either interval. Seven-item static short forms were also developed from each item bank. CONCLUSIONS: Test information curves showed that the PROMIS item banks provided substantial information in a broad range of severity, making them suitable for treatment, observational, and epidemiological research in both clinical and community settings.

Prasad, V., & Mailankody, S. (2015). How should we assess the value of innovative drugs in oncology? lessons from cost-effectiveness analyses. *Blood, 126*(15), 1860-1861.

Protopsaltis, T. S., Scheer, J. K., Terran, J. S., Smith, J. S., Hamilton, D. K., Kim, H. J., et al. (2015). How the neck affects the back: Changes in regional cervical sagittal alignment correlate to HRQOL improvement in adult thoracolumbar deformity patients at 2-year follow-up. *Journal of Neurosurgery.Spine, 23*(2), 153-158.

OBJECT Regional cervical sagittal alignment (C2-7 sagittal vertical axis [SVA]) has been shown to correlate with health-related quality of life (HRQOL). The study objective was to examine the relationship between cervical and thoracolumbar alignment parameters with HRQOL among patients with operative and nonoperative adult thoracolumbar deformity. METHODS This is a multicenter prospective data collection of consecutive patients with adult thoracolumbar spinal deformity. Clinical measures of disability included the Oswestry Disability Index (ODI), Scoliosis Research Society-22 Patient Questionnaire (SRS-22), and 36-Item Short-Form Health Survey (SF-36). Cervical radiographic parameters were correlated with global sagittal parameters within the nonoperative and operative cohorts. A partial correlation analysis was performed controlling for C-7 SVA. The operative group was subanalyzed by the magnitude of global deformity (C-7 SVA  $\geq$  5 cm vs  $<$  5 cm had significantly larger C2-7 lordosis (CL), C2-7 SVA, C-7 SVA, PI-LL, and PT than patients with a normal C-7 SVA. For all patients, baseline C2-7 SVA and CL significantly correlated with baseline ODI, Physical Component Summary (PCS), SRS Activity domain, and SRS Appearance domain. Baseline C2-7 SVA also correlated with SRS Pain and SRS Total. For the operative patients with baseline C-7 SVA  $\geq$  5 cm, the 2-year C2-7 SVA

significantly correlated with 2-year Mental Component Summary, SRS Mental, SRS Satisfaction, and decreases in ODI. Decreases in C2-7 SVA at 2 years significantly correlated with lower ODI at 2 years. Using partial correlations while controlling for C-7 SVA, the C2-7 SVA correlated significantly with baseline ODI ( $r = 0.211$ ,  $p = 0.002$ ), PCS ( $r = -0.178$ ,  $p = 0.009$ ), and SRS Activity ( $r = -0.145$ ,  $p = 0.034$ ) for the entire cohort. In the subset of operative patients with larger thoracolumbar deformities, the change in C2-7 SVA correlated with change in ODI ( $r = -0.311$ ,  $p = 0.03$ ). CONCLUSIONS Changes in cervical lordosis correlate to HRQOL improvements in thoracolumbar deformity patients at 2-year follow-up. Regional cervical sagittal parameters such as CL and C2-7 SVA are correlated with clinical measures of regional disability and health status in patients with adult thoracolumbar scoliosis. This effect may be direct or a reciprocal effect of the underlying global deformities on regional cervical alignment. However, the partial correlation analysis, controlling for the magnitude of the thoracolumbar deformity, suggests that there is a direct effect of cervical alignment on health measures. Improvements in regional cervical alignment postoperatively correlated positively with improved HRQOL.

Quinones, A. R., Talavera, G. A., Castaneda, S. F., & Saha, S. (2015). Interventions that reach into communities-promising directions for reducing racial and ethnic disparities in healthcare. *Journal of Racial and Ethnic Health Disparities*, 2(3), 336-340.

Racial/ethnic disparities in healthcare are widespread in the United States and are prevalent across healthcare organizations, including the "equal access" Veterans' Affairs (VA) integrated healthcare system. Despite substantial attention to these disparities over the last decade, there has been limited progress in reducing them. Based on a review of evidence commissioned by the VA to guide its efforts to address racial and ethnic disparities, the conceptual framework describes the root causes of disparities in healthcare quality and outcomes, demonstrating why improvements in the quality of medical care have had limited influence over healthcare disparities that depend largely on social determinants of health. The recommended interventions-including care coordination, culturally-tailored health education, and community health workers-extend the reach of health systems beyond clinics and hospitals and into the communities and social and cultural contexts in which patients live, and in which most health promotion activities occur. To make inroads into addressing disparities, healthcare systems will need to move beyond

conceptualizing care delivery as constrained to the clinical encounter and instead, incorporate an understanding of the social determinants of health.

Radiation Oncology Education Collaborative Study Group, Radiation Oncology Education Collaborative Study Group Writing Committee; Golden, D. W., Braunstein, S., Jimenez, R. B., Mohindra, P., et al. (2015). Multi-institutional implementation and evaluation of a curriculum for the medical student clerkship in radiation oncology. *Journal of the American College of Radiology : JACR*,

PURPOSE: Radiation oncology curriculum development is challenging because of limited numbers of trainees at any single institution. The goal of this project is to implement and evaluate a standardized medical student clerkship curriculum following the multi-institutional cooperative group research model. METHODS: During the 2013 academic year, a standardized curriculum was implemented at 11 academic medical centers consisting of three 1-hour lectures and a hands-on radiation treatment planning workshop. After the curriculum, students completed anonymous evaluations using Likert-type scales (1 = "not at all" to 5 = "extremely") and free responses. Evaluations asked students to rate their comfort, before and after the curriculum, with radiation oncology as a specialty, knowledge of radiotherapy planning methods, and ability to function as a radiation oncology resident. Nonparametric statistical tests were used in the analysis. RESULTS: Eighty-eight students at 11 academic medical centers completed the curriculum de novo, with a 72.7% (64 of 88) survey response rate. Fifty-seven students (89.1%) reported intent to pursue radiation oncology as their specialty. Median (interquartile range) student ratings of the importance of curricular content were as follows: overview, 4 (4-5); radiation biology/physics, 5 (4-5); practical aspects/emergencies, 5 (4-5); and planning workshop, 4 (4-5). Students reported that the curriculum helped them better understand radiation oncology as a specialty (5 [4-5]), increased specialty decision comfort (4 [3-5]), and would help the transition to radiation oncology residency (4 [4-5]). Students rated their specialty decision comfort significantly higher after completing the curriculum (4 [4-5] versus 5 [5-5];  $P < .001$ ). CONCLUSIONS: A national standardized curriculum was successfully implemented at 11 academic medical centers, providing proof of principle that curriculum development can follow the multi-institutional cooperative group research model.

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

Contribution of copy-number variation to down syndrome-associated atrioventricular septal defects. *Genetics in Medicine*, 17(7), 554-560.

Purpose: The goal of this study was to identify the contribution of large copy-number variants to Down syndrome-associated atrioventricular septal defects, the risk for which in the trisomic population is 2,000-fold more as compared with that of the general disomic population. Methods: Genome-wide copy-number variant analysis was performed on 452 individuals with Down syndrome (210 cases with complete atrioventricular septal defects; 242 controls with structurally normal hearts) using Affymetrix SNP 6.0 arrays, making this the largest heart study conducted to date on a trisomic background. Results: Large, common copy-number variants with substantial effect sizes ( $OR > 2.0$ ) do not account for the increased risk observed in Down syndrome-associated atrioventricular septal defects. By contrast, cases had a greater burden of large, rare deletions ( $P < 0.01$ ) and intersected more genes ( $P < 0.007$ ) as compared with controls. We also observed a suggestive enrichment of deletions intersecting cilium genes in cases as compared with controls. Conclusion: Our data provide strong evidence that large, rare deletions increase the risk of Down syndrome-associated atrioventricular septal defects, whereas large, common copy-number variants do not appear to increase the risk of Down syndrome-associated atrioventricular septal defects. The genetic architecture of atrioventricular septal defects is complex and multifactorial in nature. *Genet Med* 17 7, 554-560. © 2015 American College of Medical Genetics and Genomics.

Ramaker, M. J., Strong-Kaufman, M. N., Ford, M. M., Phillips, T. J., & Finn, D. A. (2015). Effect of nucleus accumbens shell infusions of ganaxolone or gaboxadol on ethanol consumption in mice. *Psychopharmacology*, 232(8), 1415-1426.

RATIONALE: Allopregnanolone (ALLO) is an endogenous neuroactive steroid thought to alter the reinforcement value of alcohol (ethanol) due to its actions as a positive modulator of the GABA<sub>A</sub> receptor (GABA<sub>A</sub>R). Extrasynaptic GABA<sub>A</sub>Rs may be a particularly sensitive target of ethanol and neuroactive steroids. Previous work showed that systemic injections of an ALLO analog, ganaxolone (GAN), or an extrasynaptic GABA<sub>A</sub>R agonist (gaboxadol; THIP) decreased ethanol intake in male mice with limited access to ethanol. OBJECTIVES: The present studies tested

whether activation of GABAARs in the nucleus accumbens (NAc) shell by GAN or THIP was sufficient to reduce ethanol intake. C57BL/6J male mice had 2-h access to 10 % ethanol (10E) and water, and 10E intake was measured following site-specific infusions of GAN or THIP. RESULTS: Decreases in limited-access 10E consumption were observed following site-specific bilateral infusions of either drug into the NAc shell. Significant changes in intake were absent when the drugs were infused in a region dorsal to the target site (GAN) or into the lateral ventricle (THIP). Locomotor data confirmed that the decreases in intake were not due to a sedative effect of the drugs. CONCLUSIONS: These data demonstrate the sufficiency of GABAAR activation by a positive allosteric modulator or an agonist with selectivity for extrasynaptic GABAARs to decrease ethanol consumption in mice. Importantly, more refined GABAAR-active targets that decrease ethanol intake may enhance our understanding and ability to treat alcohol use disorders.

Ravishankar, S., Ambady, A., Ramu, H., Mudugal, N. V., Tunduguru, R., Anbarasu, A., et al. (2015). An IPTG inducible conditional expression system for mycobacteria. *Plos One*, 10(8)

Conditional expression strains serve as a valuable tool to study the essentiality and to establish the vulnerability of a target under investigation in a drug discovery program. While essentiality implies an absolute requirement of a target function, vulnerability provides valuable information on the extent to which a target function needs to be depleted to achieve bacterial growth inhibition followed by cell death. The critical feature of an ideal conditional expression system is its ability to tightly regulate gene expression to achieve the full spectrum spanning from a high level of expression in order to support growth and near zero level of expression to mimic conditions of gene knockout. A number of bacterial conditional expression systems have been reported for use in mycobacteria. The utility of an isopropylthiogalactoside (IPTG) inducible system in mycobacteria has been reported for protein overexpression and anti-sense gene expression from a replicating multi-copy plasmid. Herein, we report the development of a versatile set of non-replicating IPTG inducible vectors for mycobacteria which can be used for generation of conditional expression strains through homologous recombination. The role of a single lac operator versus a double lac operator to regulate gene expression was evaluated by monitoring the expression levels of  $\beta$ -galactosidase in *Mycobacterium smegmatis*. These studies

indicated a significant level of leaky expression from the vector with a single lac operator but none from the vector with double lac operator. The significance of the double lac operator vector for target validation was established by monitoring the growth kinetics of an *inhA*, a *rpoB* and a *ftsZ* conditional expression strain grown in the presence of different concentrations of IPTG. The utility of this inducible system in identifying target specific inhibitors was established by screening a focussed library of small molecules using an *inhA* and a *rpoB* conditional expression strain.

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Rdesinski, R. E., Chappelle, K. G., Elliot, D. L., Litzelman, D. K., Palmer, R., & Biagioli, F. E. (2015). Development and use of an instrument adapted to assess the clinical skills learning environment in the pre-clinical years. *Medical Science Educator*, 25(3), 285-291.

**BACKGROUND:** The Communication, Curriculum, and Culture (C3) instrument is a well-established survey for measuring the professional learning climate or hidden curriculum in the clinical years of medical school. However, few instruments exist for assessing professionalism in the pre-clinical years. We adapted the C3 instrument and assessed its utility during the pre-clinical years at two U.S. medical schools. **METHODS:** The ten-item Pre-Clinical C3 survey was adapted from the C3 instrument. Surveys were administered at the conclusion of the first and second years of medical school using a repeated cross-sectional design. Factor analysis was performed and Cronbach's alphas were calculated for emerging dimensions. **RESULTS:** The authors collected 458 and 564 surveys at two medical schools during AY06-07 and AY07-09 years, respectively. Factor analysis of the survey data revealed nine items in three dimensions: "Patients as Objects", "Talking Respectfully of Colleagues", and "Patient-Centered Behaviors". Reliability measures (Cronbach's alpha) for the Pre-Clinical C3 survey data were similar to those of the C3 survey for comparable dimensions for each school. Gender analysis revealed significant differences in all three dimensions. **CONCLUSIONS:** The Pre-Clinical C3 instrument's performance was similar to the C3 instrument in measuring dimensions of professionalism. As medical education moves toward earlier and more frequent clinical and inter-professional educational

experiences, the Pre-Clinical C3 instrument may be especially useful in evaluating the impact of curricular revisions.

Redeker, N. S., Pigeon, W. R., & Boudreau, E. A. (2015). Incorporating measures of sleep quality into cancer studies. *Supportive Care in Cancer, 23*(4), 1145-1155.

Introduction/background: Sleep disturbance may influence the development of cancer and responses to treatment. It is also closely tied to recovery and quality of life in cancer patients, survivors, and caregivers, and recent studies have begun to show beneficial effects of sleep-promoting interventions. Despite the importance of sleep to cancer and its treatment and the availability of numerous tools for measuring sleep quality and quantity, sleep measurements are underutilized in cancer studies. Methods: This review, written for cancer researchers interested in incorporating sleep measures into their studies, is designed to raise awareness about the importance of sleep and suggests strategies for including sleep evaluation in cancer studies.

Conclusions: Inclusion of readily available sleep measures may ultimately improve cancer care by facilitating studies that lead to a greater understanding of how sleep and sleep disturbance influence all aspects of cancer care and the patient experience. © 2014, Springer-Verlag Berlin Heidelberg.

Reinhart, P. N., Souza, P. E., Srinivasan, N. K., & Gallun, F. J. (2015). Effects of reverberation and compression on consonant identification in individuals with hearing impairment. *Ear and Hearing, 36*(1), 1-11.

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. © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Rhode, P. R., Egan, J. O., Xu, W., Hong, H., Webb, G. M., Chen, X., et al. (2015). Comparison of the superagonist complex, ALT-803, to IL15 as cancer immunotherapeutics in animal models. *Cancer Immunology Research*,

IL15, a potent stimulant of CD8+ T cells and natural killer (NK) cells, is a promising cancer immunotherapeutic. ALT-803 is a complex of an IL15 superagonist mutant and a dimeric IL15 receptor alphaSu/Fc fusion protein that was found to exhibit enhanced biologic activity in vivo, with a substantially longer serum half-life than recombinant IL15. A single intravenous dose of ALT-803, but not IL15, eliminated well-established tumors and prolonged survival of mice bearing multiple myeloma. In this study, we extended these findings to demonstrate the superior antitumor activity of ALT-803 over IL15 in mice bearing subcutaneous B16F10 melanoma tumors and CT26 colon carcinoma metastases. Tissue biodistribution studies in mice also showed much greater retention of ALT-803 in the lymphoid organs compared with IL15, consistent with its highly potent immunostimulatory and antitumor activities in vivo. Weekly dosing with 1 mg/kg ALT-803 in C57BL/6 mice was well tolerated, yet capable of increasing peripheral blood lymphocyte, neutrophil, and monocyte counts by >8-fold. ALT-803 dose-dependent stimulation of immune cell infiltration into the lymphoid organs was also observed. Similarly, cynomolgus monkeys treated weekly with ALT-803 showed dose-dependent increases of peripheral blood

lymphocyte counts, including NK, CD4+, and CD8+ memory T-cell subsets. In vitro studies demonstrated ALT-803-mediated stimulation of mouse and human immune cell proliferation and IFN $\gamma$  production without inducing a broad-based release of other proinflammatory cytokines (i.e., cytokine storm). Based on these results, a weekly dosing regimen of ALT-803 has been implemented in multiple clinical studies to evaluate the dose required for effective immune cell stimulation in humans. *Cancer Immunol Res*; 4(1); 1-12. (c)2015 AACR.

Richardson, A. S., Meyer, K. A., Howard, A. G., Boone-Heinonen, J., Popkin, B. M., Evenson, K. R., et al. (2015). Multiple pathways from the neighborhood food environment to increased body mass index through dietary behaviors: A structural equation-based analysis in the CARDIA study. *Health and Place*, 36, 74-87.

Objectives: To examine longitudinal pathways from multiple types of neighborhood restaurants and food stores to BMI, through dietary behaviors. Methods: We used data from participants (n=5114) in the United States-based Coronary Artery Risk Development in Young Adults study and a structural equation model to estimate longitudinal (1985-86 to 2005-06) pathways simultaneously from neighborhood fast food restaurants, sit-down restaurants, supermarkets, and convenience stores to BMI through dietary behaviors, controlling for socioeconomic status (SES) and physical activity. Results: Higher numbers of neighborhood fast food restaurants and lower numbers of sit-down restaurants were associated with higher consumption of an obesogenic fast food-type diet. The pathways from food stores to BMI through diet were inconsistent in magnitude and statistical significance. Conclusions: Efforts to decrease the numbers of neighborhood fast food restaurants and to increase the numbers of sit-down restaurant options could influence diet behaviors. Availability of neighborhood fast food and sit-down restaurants may play comparatively stronger roles than food stores in shaping dietary behaviors and BMI.

Riddle, M. C., & Gerstein, H. C. (2015). Comment on hempe et al. the hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. *diabetes care* 2015;38:1067-1074. *Diabetes Care*, 38(10), e170-1.

Rose, E., & Svec, T. (2015). An evaluation of apical cracks in teeth undergoing orthograde root canal instrumentation. *Journal of Endodontics*,

INTRODUCTION: Dentinal damage and cracks induced by orthograde preparation methods have been reported in studies using extracted teeth. The purpose of this in situ investigation was to evaluate dentinal cracks in nonextracted teeth after final instrumentation. The null hypothesis is that orthograde root canal instrumentation will have no effect on crack initiation in teeth retained in the natural periodontium. METHODS: Mandibular first and second premolars of pig jaws were selected. Forty single-rooted canals were divided into 5 groups (n = 8): (1) WaveOne (Dentsply Tulsa Dental Specialties, Tulsa, OK) 25/08; (2) ProTaper rotary S1, S2, F2 (25/08) (Dentsply Tulsa Dental Specialties); (3) crown-down GT hand files 20/12, 20/10, 20/08 (Dentsply Tulsa Dental Specialties); (4) positive control (purposefully cracked); and (5) negative control (uninstrumented teeth). After instrumentation, superficial soft tissue was removed, and bone was carefully peeled away with surgical burs to the level of the root apices. Roots were resected 1 mm coronal to the working length, stained with caries indicator dye, and transilluminated; images were captured and viewed at 30x magnification to determine the presence or absence of dentinal cracks. RESULTS: WaveOne, ProTaper rotary, and GT hand files produced no cracks. All positive controls had cracks; all negative controls had no cracks. CONCLUSIONS: Within the limits of this investigation, the presence of natural periodontal structures may prevent cracking or dentinal damage in teeth receiving orthograde root canal instrumentation.

Rose, T., & Williams, D. J. (2015). Nurse leadership: The importance of balancing work with leisure. *Nurse Leader*, 13(3), 60-62.

The American Nurses Association Code of Ethics for Nurses states "the nursing profession is committed to promoting health, welfare, and safety of all people."<sup>1</sup> Nurses play an important role in promoting the health of others, yet studies indicate that many do not incorporate healthy behaviors into their own lives.<sup>2</sup> In fact, a recent article highlighted the need for nurses to practice self-care to improve their personal health and wellness, which can contribute to greater satisfaction in both their work and personal lives.<sup>3</sup> The first author of this paper (Tamara) is a registered nurse and an administrator in nursing education, whereas the second author (DJ) is an interdisciplinary social scientist whose work focuses on various forms of leisure. We have teamed

up here to discuss the importance of leisure among nurses. Healthy leisure is important among patients, yet it also remains beneficial for professionals as well. © 2015 by Elsevier Inc.

Rougas, S., Clyne, B., Cianciolo, A. T., Chan, T. M., Sherbino, J., & Yarris, L. M. (2015). An extended validity argument for assessing feedback culture. *Teaching and Learning in Medicine, 27*(4), 355-358.

NEGEA 2015 CONFERENCE ABSTRACT (EDITED) Measuring an Organization's Culture of Feedback: Can It Be Done? Steven Rougas and Brian Clyne Construct: This study sought to develop a construct for measuring formative feedback culture in an academic emergency medicine department. Four archetypes (Market, Adhocracy, Clan, Hierarchy) reflecting an organization's values with respect to focus (internal vs. external) and process (flexibility vs. stability and control) were used to characterize one department's receptiveness to formative feedback. The prevalence of residents' identification with certain archetypes served as an indicator of the department's organizational feedback culture. BACKGROUND: New regulations have forced academic institutions to implement wide-ranging changes to accommodate competency-based milestones and their assessment. These changes challenge residencies that use formative feedback from faculty as a major source of data for determining training advancement. Though various approaches have been taken to improve formative feedback to residents, there currently exists no tool to objectively measure the organizational culture that surrounds this process. Assessing organizational culture, commonly used in the business sector to represent organizational health, may help residency directors gauge their program's success in fostering formative feedback. The Organizational Culture Assessment Instrument (OCAI) is widely used, extensively validated, applicable to survey research, and theoretically based and may be modifiable to assess formative feedback culture in the emergency department. APPROACH: Using a modified Delphi technique and several iterations of focus groups amongst educators at one institution, four of the original six OCAI domains (which each contain 4 possible responses) were modified to create a 16-item Formative Feedback Culture Tool (FFCT) that was administered to 26 residents (response rate = 55%) at a single academic emergency medicine department. The mean score of each item on the FFCT (range = 0-100) was analyzed. Convergent and divergent properties of the four archetypes were assessed using a multitrait-multimethod matrix of

Pearson's coefficients. Expecting that items in one archetype would diverge from the others, whereas items within an archetype should have strong convergent properties, convergent validity was assessed by comparing items across domains that all related to the same archetype. Similarly, divergent validity was assessed by comparing the correlation of items within an archetype to the correlations of those items within a hetero-domain block (i.e., to other items within the same domain). RESULTS: Three of the four domains of the FFCT (Overall Departmental Characteristics 35.4 +/- 15.4, Departmental Foundation of Feedback 46.1 +/- 16.7, and Departmental Emphasis of Feedback 30.3 +/- 17.7) had the highest mean in the Market archetype (results/achievement oriented), whereas the final domain (Departmental Definition of Successful Feedback 34.8 +/- 22.1) had the highest mean in the Clan archetype (personal growth/team achievement). Item responses in the Clan and Hierarchy archetypes had the strongest convergent and divergent validity, respectively. Item responses in the Adhocracy archetype had the weakest convergent and divergent validity. CONCLUSIONS: Although the sample size was small, this initial study demonstrates that a modified organizational culture assessment tool can feasibly be utilized to identify the primary formative feedback archetype of a cohort of residents. This may have future implications for measuring changes in culture after the implementation of strategic programs to address formative feedback. Future studies should examine the generalizability of the FFCT to other institutions, as well as address the weak validity evidence of the Adhocracy archetype in the FFCT.

Rowland, C. M., Quinn, E. D., & Steiner, S. A. M. (2015). Beyond legal: Crafting high-quality IEPs for children with complex communication needs. *Communication Disorders Quarterly*, 37(1), 53-62. The Individualized Education Program (IEP) is a legal document developed for each student with a disability. The IEP outlines the students learning needs and associated educational goals, as well as the program placement and services required to support the attainment of these goals in the least restrictive environment. Most IEPs include all legally required elements; however, there is a gulf between meeting legal requirements and writing a high-quality IEP that results in educational benefit for the individual student. We collected a large number of IEP documents focused on interventions for children with complex communication needs (CCN) who may use augmentative and alternative communication (AAC). These documents suggested the need for a

tool to describe the subtle and specific qualities that characterize high-quality IEPs for children with CCN. We describe a 28-item IEP quality guide created to serve as a clinical resource for educators and therapists who develop educational goals. © Hammill Institute on Disabilities.

Rudmik, L., Soler, Z. M., Smith, T. L., Mace, J. C., Schlosser, R. J., & DeConde, A. S. (2015). Effect of continued medical therapy on productivity costs for refractory chronic rhinosinusitis. *JAMA Otolaryngology-- Head & Neck Surgery*, , 1-6.

Importance: It is estimated that lost productivity related to chronic rhinosinusitis (CRS) costs society in excess of \$13 billion per year in the United States. Given this tremendous cost to society, it is important to evaluate the effect of current interventions on improving this productivity loss. Objective: To define the change in productivity costs in patients with refractory CRS who select continued medical therapy. Design, Setting, and Participants: Observational cohort study. Thirty-eight patients with a guideline-based diagnosis of CRS whose initial appropriate medical therapy failed were enrolled from 4 tertiary-level rhinology clinics. The study was conducted from December 6, 2010, to April 23, 2013, and data analysis was performed from December 6, 2010, to June 1, 2015. Interventions: Continued medical therapy for CRS. Main Outcomes and Measures: The human capital approach was applied to quantify productivity costs. Absenteeism, presenteeism, and lost leisure time were quantified to define annual lost productive time, which was measured at enrollment (baseline) and at a minimum of 6 months after treatment. Lost productive time was monetized using the annual daily wage rates obtained from the 2012 US National Census and the 2013 US Department of Labor statistics. Results: Thirty-eight patients with refractory CRS who selected continued medical therapy had a mean (SD) baseline annual productivity cost of \$3464 (\$4900) per patient. After continued medical therapy for a mean of 12.8 (4.8) months, productivity costs were \$2730 (\$3720) (before vs after continued medical therapy productivity cost,  $P = .74$ ). Mean annual absenteeism was reduced from 5 (12) days to 2 (8) days ( $P = .02$ ). Mean annual presenteeism (17 [27] days reduced to 15 [23] days;  $P = .93$ ) and mean annual household days lost (7 [7] days reduced to 6 [6] days;  $P = .51$ ) were maintained at baseline levels. There were no significant differences in productivity outcomes based on endoscopy, the 22-item Sinonasal Outcome Test score, age, or polyp status (all  $P \geq .11$ ). Conclusions and Relevance: Patients with refractory CRS often make treatment

decisions based on the degree of quality-of-life and productivity impairment. Outcomes from this study suggest that productivity in patients with refractory CRS who have minor reductions in baseline productivity can remain stable with continued medical therapy. Physicians can use this information to inform appropriate patients with CRS of their expected outcomes from continued medical therapy.

Russell, D. W., & Grompe, M. (2015). Adeno-associated virus finds its disease. *Nature Genetics*, 47(10), 1104-1105.

Adeno-associated virus (AAV) vectors have been widely adopted for use in gene therapy. A new study raises concerns regarding this approach, reporting that chromosomal insertions of AAV serotype 2 seem to activate proto-oncogenes in human hepatocellular carcinoma.

Rutten, M. J., Laraway, B., Gregory, C. R., Xie, H., Renken, C., Keese, C., et al. (2015). Rapid assay of stem cell functionality and potency using electric cell-substrate impedance sensing. *Stem Cell Research & Therapy*, 6, 192-015-0182-2.

Regenerative medicine studies using autologous bone marrow mononuclear cells (BM-MNCs) have shown improved clinical outcomes that correlate to in vitro BM-MNC invasive capacity. The current Boyden-chamber assay for testing invasive capacity is labor-intensive, provides only a single time point, and takes 36 hours to collect data and results, which is not practical from a clinical cell delivery perspective. To develop a rapid, sensitive and reproducible invasion assay, we employed Electric Cell-substrate Impedance Sensing (ECIS) technology. Chemokine-directed BM-MNC cell invasion across a Matrigel-coated Transwell filter was measurable within minutes using the ECIS system we developed. This ECIS-Transwell chamber system provides a rapid and sensitive test of stem and progenitor cell invasive capacity for evaluation of stem cell functionality to provide timely clinical data for selection of patients likely to realize clinical benefit in regenerative medicine treatments. This device could also supply robust unambiguous, reproducible and cost effective data as a potency assay for cell product release and regulatory strategies.

Ryan, M. C., Ostmo, S., Jonas, K., Berrocal, A., Drenser, K., Horowitz, J., et al. (2014). Development and evaluation of reference standards for image-based telemedicine diagnosis and clinical

research studies in ophthalmology. *AMIA ...Annual Symposium Proceedings / AMIA Symposium*. AMIA Symposium, 2014, 1902-1910.

Information systems managing image-based data for telemedicine or clinical research applications require a reference standard representing the correct diagnosis. Accurate reference standards are difficult to establish because of imperfect agreement among physicians, and discrepancies between clinical vs. image-based diagnosis. This study is designed to describe the development and evaluation of reference standards for image-based diagnosis, which combine diagnostic impressions of multiple image readers with the actual clinical diagnoses. We show that agreement between image reading and clinical examinations was imperfect (689 [32%] discrepancies in 2148 image readings), as was inter-reader agreement ( $\kappa$  0.490-0.652). This was improved by establishing an image-based reference standard defined as the majority diagnosis given by three readers (13% discrepancies with image readers). It was further improved by establishing an overall reference standard that incorporated the clinical diagnosis (10% discrepancies with image readers). These principles of establishing reference standards may be applied to improve robustness of real-world systems supporting image-based diagnosis.

Saitz, T. R., & Serefoglu, E. C. (2015). Advances in understanding and treating premature ejaculation. *Nature Reviews.Urology*,

Over the past several years, many advances have been made in our understanding of the epidemiology, pathophysiology, and management of premature ejaculation. Newly developed definitions of premature ejaculation are now available, and our perception of the classification, prevalence, aetiological factors, and treatment options for premature ejaculation have evolved. Despite ongoing research, there remains much to be learned about all aspects of this common sexual disorder, in particular effective clinical diagnosis and treatment options.

Saultz, J. (2015). Engaging patients and communities. *Family Medicine*, 47(9), 677-678.

Saunders, G. H., & Chisolm, T. H. (2015). Connected audiological rehabilitation: 21st century innovations. *Journal of the American Academy of Audiology*, 26(9), 768-776.

BACKGROUND: Tele-audiology provides a means to offer audiological rehabilitation (AR) in a cost-, resource-, and time-effective manner. If designed appropriately, it also has the capability of

personalizing rehabilitation to the user in terms of content, depth of detail, etc., thus permitting selection of the best content for a particular individual. Synchronous/real-time data collection, store and forward telehealth, remote monitoring and mobile health using smartphone applications have each been applied to components of audiologic rehabilitation intervention (sensory management, instruction in the use of technology and control of the listening environment, perceptual and communication strategies training, and counseling). In this article, the current state of tele-audiological rehabilitation interventions are described and discussed. RESULTS: The provision of AR via tele-audiology potentially provides a cost-effective mechanism for addressing barriers to the routine provision of AR beyond provisions of hearing technology. Furthermore, if designed appropriately, it has the capability of personalizing rehabilitation to the user in terms of content, depth of detail, etc., thus permitting selection of the best content for a particular individual. However, effective widespread implementation of tele-audiology will be dependent on good education of patients and clinician alike, and researchers must continue to examine the effectiveness of these new approaches to AR in order to ensure clinicians provide effective evidence-based rehabilitation to their patients. CONCLUSIONS: While several barriers to the widespread use of tele-audiology for audiologic rehabilitation currently exist, it is concluded that through education of patients and clinicians alike, it will gain greater support from practitioners and patients over time and will become successfully and widely implemented.

Sayer, N. A., Noorbaloochi, S., Frazier, P. A., Pennebaker, J. W., Orazem, R. J., Schnurr, P. P., et al. (2015). Randomized controlled trial of online expressive writing to address readjustment difficulties among U.S. afghanistan and iraq war veterans. *Journal of Traumatic Stress, 28*(5), 381-390.

We examined the efficacy of a brief, accessible, nonstigmatizing online intervention-writing expressively about transitioning to civilian life. U.S. Afghanistan and Iraq war veterans with self-reported reintegration difficulty (N = 1,292, 39.3% female, M = 36.87, SD = 9.78 years) were randomly assigned to expressive writing (n = 508), factual control writing (n = 507), or no writing (n = 277). Using intention to treat, generalized linear mixed models demonstrated that 6-months postintervention, veterans who wrote expressively experienced greater reductions in physical complaints, anger, and distress compared with veterans who wrote factually (ds = 0.13

to 0.20;  $ps < .05$ ) and greater reductions in PTSD symptoms, distress, anger, physical complaints, and reintegration difficulty compared with veterans who did not write at all ( $ds = 0.22$  to  $0.35$ ;  $ps \leq .001$ ). Veterans who wrote expressively also experienced greater improvement in social support compared to those who did not write ( $d = 0.17$ ). Relative to both control conditions, expressive writing did not lead to improved life satisfaction. Secondary analyses also found beneficial effects of expressive writing on clinically significant distress, PTSD screening, and employment status. Online expressive writing holds promise for improving health and functioning among veterans experiencing reintegration difficulty, albeit with small effect sizes. © 2015 International Society for Traumatic Stress Studies.

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

Postoperative recovery after adult spinal deformity surgery: Comparative analysis of age in 149 patients during 2-year follow-up. *Spine*, 40(19), 1505-1515.

Postoperative recovery was calculated based on normalized outcome scores and an integrated health state analysis. Both elderly patients and those with high preoperative baseline disability had a shorter and improved recovery period compared with younger patients or patients with low baseline disability when normalized to their preoperative baseline values. Study Design.

Retrospective review of a multicenter, prospective adult spinal deformity (ASD) database.

Objective. We hypothesized that increased age and increased preoperative disability would negatively impact both the length of time needed to achieve maximal recovery and the amount of functional improvement achieved. In order to gauge the recovery process, a normalization process was used to calculate an integrated health state (IHS) during the 2-year postoperative period. Summary of Background Data. Elderly patients with ASD generally have worse baseline health-related quality of life (HRQOL) measures than younger patients. Current methods of reporting outcomes are limited, perhaps diminishing the health impact of the entire postoperative recovery experience. Methods. Inclusion criteria included 18 or more years and ASD. Patient groups: young ( $\leq 45$  yr), middle (46-64), elderly ( $\geq 65$ ) as well as by baseline Oswestry Disability Index (ODI) scores: MILD (0-30), MEDIUM (31-49), and HIGH ( $\geq 50$ ). Collected HRQOL measures included ODI, Short Form-36(PCS/MCS), and Scoliosis Research Society-22 (SRS22) at baseline, 6 weeks, 1, and 2-year postoperative. All HRQOL measures were normalized to each patient's

baseline scores. A 2-year IHS was calculated for each individual patient and the means were compared between groups. Results. 149 patients were included ( $\leq 45:32$ ,  $46-64:67$ ,  $\geq 65:50$ ). All groups significantly improved in all HRQOL at 2-year compared with baseline (P 0.05). Normalized IHS HRQOL for young patients was worse than elderly for ODI, PCS, MCS, SRS activity, pain and total during the 2-year recovery period from index surgery. The MILD ODI group had significantly worse 2-year IHS values than the HIGH group for all HRQOL measured (P 0.05). Conclusion. Contrary to our hypothesis, an IHS analysis suggested that the recovery process was significantly better for elderly patients than young patients and better for patients with high baseline disability. © 2015 Wolters Kluwer Health, Inc.

Sherman, L. S., Matsumoto, S., Su, W., Srivastava, T., & Back, S. A. (2015). Hyaluronan synthesis, catabolism, and signaling in neurodegenerative diseases. *International Journal of Cell Biology*, 2015, 368584.

The glycosaminoglycan hyaluronan (HA), a component of the extracellular matrix, has been implicated in regulating neural differentiation, survival, proliferation, migration, and cell signaling in the mammalian central nervous system (CNS). HA is found throughout the CNS as a constituent of proteoglycans, especially within perineuronal nets that have been implicated in regulating neuronal activity. HA is also found in the white matter where it is diffusely distributed around astrocytes and oligodendrocytes. Insults to the CNS lead to long-term elevation of HA within damaged tissues, which is linked at least in part to increased transcription of HA synthases. HA accumulation is often accompanied by elevated expression of at least some transmembrane HA receptors including CD44. Hyaluronidases that digest high molecular weight HA into smaller fragments are also elevated following CNS insults and can generate HA digestion products that have unique biological activities. A number of studies, for example, suggest that both the removal of high molecular weight HA and the accumulation of hyaluronidase-generated HA digestion products can impact CNS injuries through mechanisms that include the regulation of progenitor cell differentiation and proliferation. These studies, reviewed here, suggest that targeting HA synthesis, catabolism, and signaling are all potential strategies to promote CNS repair.

Shi, Z., Cassaglia, P. A., Gotthardt, L. C., & Brooks, V. L. (2015). Hypothalamic paraventricular and arcuate nuclei contribute to elevated sympathetic nerve activity in pregnant rats: Roles of neuropeptide Y and alpha-melanocyte-stimulating hormone. *Hypertension*,

Pregnancy increases sympathetic nerve activity (SNA), but the mechanisms are unknown. Here, we investigated the contributions of the hypothalamic paraventricular and arcuate nuclei in alpha-chloralose-anesthetized pregnant and nonpregnant rats. Baseline arterial pressure (AP) was lower, and heart rate (HR), lumbar sympathetic activity, and splanchnic SNA were higher in pregnant rats compared with nonpregnant rats. Inhibition of the paraventricular nucleus via bilateral muscimol nanoinjections decreased AP and HR more in pregnant rats than in nonpregnant rats and decreased lumbar SNA only in pregnant rats. Similarly, after arcuate muscimol nanoinjections, the decreases in AP, HR, and lumbar, renal, and splanchnic sympathetic nerve activities were greater in pregnant rats than in nonpregnant rats. Major arcuate neuronal groups that project to the paraventricular nucleus express inhibitory neuropeptide Y (NPY) and excitatory alpha-melanocyte-stimulating hormone. Inhibition of paraventricular melanocortin 3/4 receptors with SHU9119 also decreased AP, HR, and lumbar SNA in pregnant rats but not in nonpregnant rats. Conversely, paraventricular nucleus NPY expression was reduced in pregnant animals, and although blockade of paraventricular NPY Y1 receptors increased AP, HR, and lumbar sympathetic activity in nonpregnant rats, it had no effects in pregnant rats. Yet, the sympathoinhibitory, depressor, and bradycardic effects of paraventricular NPY nanoinjections were similar between groups. In conclusion, the paraventricular and arcuate nuclei contribute to increased basal SNA during pregnancy, likely due in part to decreased tonic NPY inhibition and increased tonic alpha-melanocyte-stimulating hormone excitation of presympathetic neurons in the paraventricular nucleus.

Sieper, J., Kivitz, A., Van Tubergen, A., Deodhar, A., Coteur, G., Woltering, F., et al. (2015). Impact of certolizumab pegol on patient-reported outcomes in patients with axial spondyloarthritis. *Arthritis Care and Research*, 67(10), 1475-1480.

Objective Patient-reported outcomes (PROs) provide an opportunity to collect important information relating to patient well-being, which is often difficult for physicians to measure (e.g., quality of life, pain, fatigue, and sleep). Here we evaluate the effects of certolizumab pegol (CZP)

on PROs during the 24-week, double-blind phase of the RAPID axial spondyloarthritis (SpA) trial, a phase 3 trial of axial SpA patients, including both ankylosing spondylitis (AS) and nonradiographic axial SpA patients. Methods A total of 325 patients with active axial SpA were randomized 1:1:1 to placebo, CZP 200 mg every 2 weeks, or CZP 400 mg every 4 weeks. The primary end point was the Assessment of SpondyloArthritis International Society criteria for 20% improvement in disease activity response at week 12, and has been reported previously. PROs included total back pain, nocturnal back pain, a daily pain diary, the Sleep Problems Index II (SPI) domain of the Medical Outcomes Study (MOS) Sleep Scale, fatigue, the Ankylosing Spondylitis Quality of Life (ASQOL) measure, and the Short Form 36-item (SF-36) health survey physical component summary (PCS), mental component summary (MCS), and domains. Results Patients treated with CZP reported significant improvements from week 1 for nocturnal back pain (placebo -0.6, CZP 200 mg every 2 weeks -1.9, and CZP 400 mg every 4 weeks -1.6;  $P < 0.001$ ) and ASQOL (placebo -1.0, CZP 200 mg every 2 weeks -2.3, and CZP 400 mg every 4 weeks -1.9;  $P < 0.05$ ) compared with placebo, while significant improvements in total back pain were seen from day 2. Patients treated with both CZP dosing regimens also had significantly greater improvements in fatigue, MOS-SPI, SF-36 PCS, MCS, and domains compared with placebo. Improvements were similar in both AS and nonradiographic axial SpA patients. Conclusion Both CZP dosing schedules rapidly improved patient well-being, as measured by PROs, including pain, fatigue, sleep, SF-36, and ASQOL in both AS and nonradiographic axial SpA patients. © 2015 The Authors. Arthritis Care & Research is published by Wiley Periodicals, Inc. on behalf of the American College of Rheumatology.

Simon, M. J., & Iliff, J. J. (2015). Regulation of cerebrospinal fluid (CSF) flow in neurodegenerative, neurovascular and neuroinflammatory disease. *Biochimica Et Biophysica Acta*, Cerebrospinal fluid (CSF) circulation and turnover provides a sink for the elimination of solutes from the brain interstitium, serving an important homeostatic role for the function of the central nervous system. Disruption of normal CSF circulation and turnover is believed to contribute to the development of many diseases, including neurodegenerative conditions such as Alzheimer's disease, ischemic and traumatic brain injury, and neuroinflammatory conditions such as multiple sclerosis. Recent insights into CSF biology suggesting that CSF and interstitial fluid exchange

along a brain-wide network of perivascular spaces termed the 'glymphatic' system suggest that CSF circulation may interact intimately with glial and vascular function to regulate basic aspects of brain function. Dysfunction within this glial vascular network, which is a feature of the aging and injured brain, is a potentially critical link between brain injury, neuroinflammation and the development of chronic neurodegeneration. Ongoing research within this field may provide a powerful new framework for understanding the common links between neurodegenerative, neurovascular and neuroinflammatory disease, in addition to providing potentially novel therapeutic targets for these conditions. This article is part of a Special Issue entitled: Neuro inflammation: A common denominator for stroke, multiple sclerosis and Alzheimer's disease, guest edited by Helga de Vries and Markus Swanger.

Simpson, M. A., de la Motte, C., Sherman, L. S., & Weigel, P. H. (2015). Advances in hyaluronan biology: Signaling, regulation, and disease mechanisms. *International Journal of Cell Biology*, 2015, 690572.

Skalsky, R. L., & Cullen, B. R. (2015). EBV noncoding RNAs. *Current Topics in Microbiology and Immunology*, 391, 181-217.

EBV expresses a number of viral noncoding RNAs (ncRNAs) during latent infection, many of which have known regulatory functions and can post-transcriptionally regulate viral and/or cellular gene expression. With recent advances in RNA sequencing technologies, the list of identified EBV ncRNAs continues to grow. EBV-encoded RNAs (EBERs) , the BamHI-A rightward transcripts (BARTs) , a small nucleolar RNA (snoRNA) , and viral microRNAs (miRNAs) are all expressed during EBV infection in a variety of cell types and tumors. Recently, additional novel EBV ncRNAs have been identified. Viral miRNAs, in particular, have been under extensive investigation since their initial identification over ten years ago. High-throughput studies to capture miRNA targets have revealed a number of miRNA-regulated viral and cellular transcripts that tie into important biological networks. Functions for many EBV ncRNAs are still unknown; however, roles for many EBV miRNAs in latency and in tumorigenesis have begun to emerge. Ongoing mechanistic studies to elucidate the functions of EBV ncRNAs should unravel additional roles for ncRNAs in the viral life cycle. In this chapter, we will discuss our current knowledge of the types of ncRNAs

expressed by EBV, their potential roles in viral latency, and their potential involvement in viral pathogenesis.

Smith, M. W., Davis, R. E., Youngblut, N. D., Karna, T., Herfort, L., Whitaker, R. J., et al. (2015).

Metagenomic evidence for reciprocal particle exchange between the mainstem estuary and lateral bay sediments of the lower Columbia River. *Frontiers in Microbiology*, 6, 1074.

Lateral bays of the lower Columbia River estuary are areas of enhanced water retention that influence net ecosystem metabolism through activities of their diverse microbial communities. Metagenomic characterization of sediment microbiota from three disparate sites in two brackish lateral bays (Baker and Youngs) produced approximately 100 Gbp of DNA sequence data analyzed subsequently for predicted SSU rRNA and peptide-coding genes. The metagenomes were dominated by Bacteria. A large component of Eukaryota was present in Youngs Bay samples, i.e., the inner bay sediment was enriched with the invasive New Zealand mudsnail, *Potamopyrgus antipodarum*, known for high ammonia production. The metagenome was also highly enriched with an archaeal ammonia oxidizer closely related to *Nitrosoarchaeum limnia*. Combined analysis of sequences and continuous, high-resolution time series of biogeochemical data from fixed and mobile platforms revealed the importance of large-scale reciprocal particle exchanges between the mainstem estuarine water column and lateral bay sediments. Deposition of marine diatom particles in sediments near Youngs Bay mouth was associated with a dramatic enrichment of Bacteroidetes (58% of total Bacteria) and corresponding genes involved in phytoplankton polysaccharide degradation. The Baker Bay sediment metagenome contained abundant Archaea, including diverse methanogens, as well as functional genes for methylotrophy and taxonomic markers for syntrophic bacteria, suggesting that active methane cycling occurs at this location. Our previous work showed enrichments of similar anaerobic taxa in particulate matter of the mainstem estuarine water column. In total, our results identify the lateral bays as both sources and sinks of biogenic particles significantly impacting microbial community composition and biogeochemical activities in the estuary.

Snowden, J. M., Mortimer, K. M., Kang Dufour, M. -, & Tager, I. B. (2015). Population intervention models to estimate ambient NO<sub>2</sub> health effects in children with asthma. *Journal of Exposure*

*Science and Environmental Epidemiology*, 25(6), 567-573.

Health effects of ambient air pollution are most frequently expressed in individual studies as responses to a standardized unit of air pollution changes (e.g., an interquartile interval), which is thought to enable comparison of findings across studies. However, this approach does not necessarily convey health effects in terms of a real-world air pollution scenario. In the present study, we use population intervention modeling to estimate the effect of an air pollution intervention that makes explicit reference to the observed exposure data and is identifiable in those data. We calculate the association between ambient summertime nitrogen dioxide (NO<sub>2</sub>) and forced expiratory flow between 25% and 75% of forced vital capacity (FEF 25-75) in a cohort of children with asthma in Fresno, California. We scale the effect size to reflect NO<sub>2</sub> abatement on a majority of summer days. The effect estimates were small, imprecise, and consistently indicated improved pulmonary function with decreased NO<sub>2</sub>. The effects ranged from -0.8% of mean FEF 25-75 (95% confidence interval (CI): -3.4, 1.7) to -3.3% (95% CI: -7.5, 0.9). We conclude by discussing the nature and feasibility of the exposure change analyzed here given the observed air pollution profile, and we propose additional applications of population intervention models in environmental epidemiology. © 2015 Nature America, Inc. All rights reserved.

Sonnenberg, A., & Genta, R. M. (2015). Low prevalence of colon polyps in chronic inflammatory conditions of the colon. *The American Journal of Gastroenterology*, 110(7), 1056-1061.

**OBJECTIVES:** Previous studies have reported a low prevalence of colon polyps in patients with microscopic colitis. The aim of the study was to test whether such inverse associations applied to other inflammatory diseases of the colon. **METHODS:** In a case-control study among 130,204 patients undergoing colonoscopy for the work-up of diarrhea, we compared the prevalence of colon polyps in a case population of patients with inflammatory bowel disease (IBD), microscopic colitis, histologic signs of active colitis, diverticulitis, or ischemic colitis, and in a control population with normal colon mucosa. Case and control subjects were compared using odds ratios and their 95% confidence intervals adjusted for age and sex. **RESULTS:** In 11,176 patients with microscopic colitis, the prevalence of hyperplastic polyps, serrated adenomas, and tubular adenomas were all reduced: odds ratios=0.46 (95% confidence intervals=0.43-0.49), 0.24 (0.19-0.30), and 0.35 (0.33-0.38), respectively. In 4,435 patients with IBD, the corresponding

values were: 0.18 (0.15-0.21), 0.24 (0.16-0.35), and 0.18 (0.15-0.21), respectively. In 6,501 patients with histologically active colitis, the corresponding values were: 0.58 (0.53-0.63), 0.57 (0.46-0.70), and 0.63 (0.58-0.68), respectively. No such consistent reduction in polyp prevalence was found in patients with diverticulitis or ischemic colitis. CONCLUSIONS: Chronic inflammatory conditions of the colon are associated with a decreased prevalence of colon polyps.

Stankoska, K., Sarram, L., Smith, S., Bedran-Russo, A. K., Little, C. B., Swain, M. V., et al. (2015).

Immunolocalization and distribution of proteoglycans in carious dentine. *Australian Dental Journal*,

Type I collagen, proteoglycans (PG) and non-collagenous proteins represent important building blocks of the dentine matrix. While different PGs have been identified in dentine, changes in the distribution of these macromolecules with the progression of caries have been poorly characterized. The aim of this study was to compare the immunolocalization of three small collagen-binding PGs (biglycan, fibromodulin and lumican) as well as collagen (types I and VI) in healthy versus carious dentine. Longitudinal demineralized sections of extracted teeth were stained with antibodies recognizing specific PG core proteins and collagens, as well as glycosaminoglycans (GAGs) with toluidine blue. In healthy dentine, PGs appeared to be more abundant near the tubule walls and directly under the cusps. Conversely, in carious dentine, specific locations appeared to be more prone to PG degradation than others. These degradation patterns were well correlated with the progression of caries into the tissue, and also appeared to trigger interesting morphological changes in the tissue structure, such as the deformation of dentine tubules near highly infected areas and the lower concentration of PG in tertiary dentine. This study presents new insights into the involvement of PGs in the progression of caries. This article is protected by copyright. All rights reserved.

Stecker, E. C., Ayanian, J. Z., & Fendrick, A. M. (2015). Value-based insurance design: Aligning incentives to improve cardiovascular care. *Circulation*, 132(16), 1580-1585.

Stephens, D. M., & Spurgeon, S. E. (2015). Ibrutinib in mantle cell lymphoma patients: Glass half full? evidence and opinion. *Therapeutic Advances in Hematology*, 6(5), 242-252.

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin's lymphoma typically marked by an

aggressive clinical course and a predilection for relapse. The B-cell receptor (BCR) signaling survival pathway is chronically activated in MCL, contributing to its pathogenesis. Ibrutinib is an inhibitor of Bruton's tyrosine kinase, a vital component of this pathway. This article details the current clinical experience with ibrutinib in the treatment of patients with MCL, including completed and published clinical trials and reviews potential adverse events (AEs) and pitfalls associated with ibrutinib therapy. Although most AEs experienced by patients treated with ibrutinib are mild, some can be severe and treatment limiting and may be attributed to off-target effects. Ibrutinib is a very promising agent for patients with MCL with notable response rates. However, when used as a single agent, around one third of patients relapse in the first 2 years of treatment. Recently reported combination therapies have shown significant activity. Emerging data evaluating potential mechanisms of drug resistance and the poor clinical outcomes after treatment failure are also discussed. Further understanding of resistance and its implications not only in relapsed disease but in the frontline setting are needed. Investigation of strategies to overcome resistance remains an area of high unmet clinical need. Evaluation of the impact of shorter treatment duration, effects on minimal residual disease, and incorporation of novel combinations are also warranted.

Stockler-Ipsiroglu, S., Apatean, D., Battini, R., DeBrosse, S., Dessoffy, K., Edvardson, S., et al.

(2015). Arginine:Glycine amidinotransferase (AGAT) deficiency: Clinical features and long term outcomes in 16 patients diagnosed worldwide. *Molecular Genetics and Metabolism*,  
BACKGROUND: Arginine:glycine aminotransferase (AGAT) (GATM) deficiency is an autosomal recessive inborn error of creatine synthesis. OBJECTIVE: We performed an international survey among physicians known to treat patients with AGAT deficiency, to assess clinical characteristics and long-term outcomes of this ultra-rare condition. RESULTS: 16 patients from 8 families of 8 different ethnic backgrounds were included. 1 patient was asymptomatic when diagnosed at age 3weeks. 15 patients diagnosed between 16months and 25years of life had intellectual disability/developmental delay (IDD). 8 patients also had myopathy/proximal muscle weakness. Common biochemical denominators were low/undetectable guanidinoacetate (GAA) concentrations in urine and plasma, and low/undetectable cerebral creatine levels. 3 families had protein truncation/null mutations. The rest had missense and splice mutations. Treatment with

creatine monohydrate (100-800mg/kg/day) resulted in almost complete restoration of brain creatine levels and significant improvement of myopathy. The 2 patients treated since age 4 and 16months had normal cognitive and behavioral development at age 10 and 11years. Late treated patients had limited improvement of cognitive functions. CONCLUSION: AGAT deficiency is a treatable intellectual disability. Early diagnosis may prevent IDD and myopathy. Patients with unexplained IDD with and without myopathy should be assessed for AGAT deficiency by determination of urine/plasma GAA and cerebral creatine levels (via brain MRS), and by GATM gene sequencing.

Stone, L. A., & Harshbarger, R. J.,3rd. (2015). Orbital necrotizing fasciitis and osteomyelitis caused by arcanobacterium haemolyticum: A case report. *Ophthalmic Plastic and Reconstructive Surgery*, 31(2), e31-e33.

The facial region is infrequently affected by necrotizing infections. Orbital necrotizing infections are even rarer, seen following trauma, local skin infection, and sinusitis. The authors report a unique case of orbital necrotizing fasciitis and osteomyelitis resulting from Arcanobacterium Haemolyticum ethmoid sinusitis. No prior occurrences of Arcanobacterial species orbital necrotizing fasciitis/osteomyelitis have been reported. A 16-year-old boy presented to the ER with a 3-day history of fever, chills, headache, and sinus pressure. CT scan revealed soft tissue swelling of the right orbit, forehead, and ethmoid sinusitis. Within 24 hours of admission, he suffered rapidly progressive swelling and erythema of the right orbit and forehead with diminished visual acuity, despite broad-spectrum antibiotics. Orbital exploration revealed frankly necrotic fascia and periosteum along the superior aspect. Lateral canthotomy, cantholysis, decompression of the optic nerve, and soft tissue debridement with bone biopsy was performed. Operative specimens isolated Arcanobacterium Haemolyticum. Pathologic examination revealed right orbital osteomyelitis.

Suhag, A., Reina, J., Sanapo, L., Martinelli, P., Saccone, G., Simonazzi, G., et al. (2015). Prior ultrasound-indicated cerclage: Comparison of cervical length screening or history-indicated cerclage in the next pregnancy. *Obstetrics and Gynecology*, 126(5), 962-968.

OBJECTIVE: To evaluate outcomes of women with prior ultrasound-indicated cerclage, who in

their subsequent pregnancy were either followed by transvaginal ultrasound cervical length screening or received a planned history-indicated cerclage. METHODS: Multicenter cohort study of singleton gestations with a prior ultrasound-indicated cerclage performed from 1994 to 2014. We evaluated three pregnancies in the study participants: first pregnancy with prior spontaneous preterm birth at less than 37 weeks of gestation; second pregnancy with ultrasound-indicated cerclage for cervical length 25 mm or less; and the third index pregnancy managed with either transvaginal ultrasound cervical length screening with ultrasound-indicated cerclage for cervical length 25 mm or less or planned history-indicated cerclage. The primary outcome was incidence of spontaneous preterm birth at less than 37 weeks of gestation. We planned a subgroup analysis for women who delivered at less than 32 weeks of gestation compared with 32 weeks of gestation or greater in their prior ultrasound-indicated cerclage pregnancy. RESULTS: Of 102 singleton gestations included, 38 (37.3%) were followed with transvaginal ultrasound cervical length screening and 64 (62.7%) underwent history-indicated cerclage. Of 38 women in the transvaginal ultrasound group, 18 (47.4%) underwent ultrasound-indicated cerclage for cervical length 25 mm or less. After adjusting for confounders, the rate of spontaneous preterm birth at less than 37 weeks of gestation was similar between transvaginal ultrasound cervical length screening and history-indicated cerclage groups (36.8% compared with 43.8%; adjusted odds ratio 0.77, 95% confidence interval 0.47-1.45). Secondary outcomes were also similar in both groups. All women (n=7) who delivered at less than 32 weeks of gestation in their prior pregnancy and subsequently had transvaginal ultrasound screening received ultrasound-indicated cerclage in the index pregnancy compared with only 35.5% of women who delivered at 32 weeks of gestation or greater in their prior pregnancy. CONCLUSION: Women with prior ultrasound-indicated cerclage have similar outcomes if they receive either transvaginal ultrasound cervical length screening with ultrasound-indicated cerclage for cervical length 25 mm or less or planned history-indicated cerclage in the subsequent pregnancy. Less than 50% of the transvaginal ultrasound cervical length screening group require a repeat ultrasound-indicated cerclage in the subsequent pregnancy. LEVEL OF EVIDENCE: II.

Sullivan, D. R., & Slatore, C. G. (2015). Advance care planning. does it benefit surrogate decision makers in the intensive care unit? *Annals of the American Thoracic Society*, 12(10), 1432-1433.

Sullivan, J. P., Munch, J., O' Sullivan, E., & Kelly, B. T. (2015). Femoroacetabular impingement. (pp. 99-117) Springer International Publishing.

Femoroacetabular impingement (FAI) results from abnormal contact between the acetabulum and the femur. Femoral-sided impingement, also known as cam impingement, damages the labrum and intra-articular cartilage as the aspherical femoral head reaches terminal range of motion. Pincer impingement occurs due to acetabular over coverage, which may be focal or global, and damages the labrum as the excess rim impacts against the femoral neck. Both cam and pincer impingement limit hip range of motion and cause repetitive edge loading. This results in progressive labral injury, chondral injury, and hip degeneration that is irreversible [1]. © Springer International Publishing Switzerland 2015.

Sun, B., Guan, X., Fang, J., & Tratnyek, P. G. (2015). Activation of manganese oxidants with bisulfite for enhanced oxidation of organic contaminants: The involvement of Mn(III). *Environmental Science & Technology*, 49(20), 12414-12421.

MnO<sub>4</sub><sup>(-)</sup> was activated by HSO<sub>3</sub><sup>(-)</sup>, resulting in a process that oxidizes organic contaminants at extraordinarily high rates. The permanganate/bisulfite (PM/BS) process oxidized phenol, ciprofloxacin, and methyl blue at pH 5.0 with rates (k<sub>obs</sub> approximately 60-150 s<sup>(-1)</sup>) that were 5-6 orders of magnitude faster than those measured for permanganate alone, and approximately 5 to 7 orders of magnitude faster than conventional advanced oxidation processes for water treatment. Oxidation of phenol was fastest at pH 4.0, but still effective at pH 7.0, and only slightly slower when performed in tap water. A smaller, but still considerable (approximately 3 orders of magnitude) increase in oxidation rates of methyl blue was observed with MnO<sub>2</sub> activated by HSO<sub>3</sub><sup>(-)</sup> (MO/BS). The above results, time-resolved spectroscopy of manganese species under various conditions, stoichiometric analysis of pH changes, and the effect of pyrophosphate on UV absorbance spectra suggest that the reactive intermediate(s) responsible for the extremely rapid oxidation of organic contaminants in the PM/BS process involve manganese(III) species with minimal stabilization by complexation. The PM/BS process may lead to a new category of advanced oxidation technologies based on contaminant oxidation by reactive manganese(III) species, rather than hydroxyl and sulfate radicals.

Teo, A. R., Choi, H., Andrea, S. B., Valenstein, M., Newsom, J. T., Dobscha, S. K., et al. (2015). Does mode of contact with different types of social relationships predict depression in older adults? evidence from a nationally representative survey. *Journal of the American Geriatrics Society*, 63(10), 2014-2022.

**OBJECTIVES:** To determine associations between use of three different modes of social contact (in person, telephone, written or e-mail), contact with different types of people, and risk of depressive symptoms in a nationally representative, longitudinal sample of older adults. **DESIGN:** Population-based observational cohort. **SETTING:** Urban and suburban communities throughout the contiguous United States. **PARTICIPANTS:** Individuals aged 50 and older who participated in the Health and Retirement Survey between 2004 and 2010 (N = 11,065). **MEASUREMENTS:** Frequency of participant use of the three modes of social contact with children, other family members, and friends at baseline were used to predict depressive symptoms (measured using the eight-item Center for Epidemiologic Studies Depression Scale) 2 years later using multivariable logistic regression models. **RESULTS:** Probability of having depressive symptoms steadily increased as frequency of in-person-but not telephone or written or e-mail contact-decreased. After controlling for demographic, clinical, and social variables, individuals with in-person social contact every few months or less with children, other family, and friends had a significantly higher probability of clinically significant depressive symptoms 2 years later (11.5%) than those having in-person contact once or twice per month (8.1%;  $P < .001$ ) or once or twice per week (7.3%;  $P < .001$ ). Older age, interpersonal conflict, and depression at baseline moderated some of the effects of social contact on depressive symptoms. **CONCLUSION:** Frequency of in-person social contact with friends and family independently predicts risk of subsequent depression in older adults. Clinicians should consider encouraging face-to-face social interactions as a preventive strategy for depression.

Teo, A. R., Fetters, M. D., Stufflebam, K., Tateno, M., Balhara, Y., Choi, T. Y., et al. (2015).

Identification of the hikikomori syndrome of social withdrawal: Psychosocial features and treatment preferences in four countries. *The International Journal of Social Psychiatry*, 61(1), 64-72.

**BACKGROUND:** Hikikomori, a form of social withdrawal first reported in Japan, may exist globally

but cross-national studies of cases of hikikomori are lacking. AIMS: To identify individuals with hikikomori in multiple countries and describe features of the condition. METHOD: Participants were recruited from sites in India, Japan, Korea and the United States. Hikikomori was defined as a 6-month or longer period of spending almost all time at home and avoiding social situations and social relationships, associated with significant distress/impairment. Additional measures included the University of California, Los Angeles (UCLA) Loneliness Scale, Lubben Social Network Scale (LSNS-6), Sheehan Disability Scale (SDS) and modified Cornell Treatment Preferences Index. RESULTS: A total of 36 participants with hikikomori were identified, with cases detected in all four countries. These individuals had high levels of loneliness (UCLA Loneliness Scale  $M = 55.4$ ,  $SD = 10.5$ ), limited social networks (LSNS-6  $M = 9.7$ ,  $SD = 5.5$ ) and moderate functional impairment (SDS  $M = 16.5$ ,  $SD = 7.9$ ). Of them 28 (78%) desired treatment for their social withdrawal, with a significantly higher preference for psychotherapy over pharmacotherapy, in-person over telepsychiatry treatment and mental health specialists over primary care providers. Across countries, participants with hikikomori had similar generally treatment preferences and psychosocial features. CONCLUSION: Hikikomori exists cross-nationally and can be assessed with a standardized assessment tool. Individuals with hikikomori have substantial psychosocial impairment and disability, and some may desire treatment.

Terker, A. S., Zhang, C., Erspamer, K. J., Gamba, G., Yang, C. L., & Ellison, D. H. (2015). Unique chloride-sensing properties of WNK4 permit the distal nephron to modulate potassium homeostasis. *Kidney International*,  
Dietary potassium deficiency activates thiazide-sensitive sodium chloride cotransport along the distal nephron. This may explain, in part, the hypertension and cardiovascular mortality observed in individuals who consume a low-potassium diet. Recent data suggest that plasma potassium affects the distal nephron directly by influencing intracellular chloride, an inhibitor of the with-no-lysine kinase (WNK)-Ste20p-related proline- and alanine-rich kinase (SPAK) pathway. As previous studies used extreme dietary manipulations, we sought to determine whether the relationship between potassium and NaCl cotransporter (NCC) is physiologically relevant and clarify the mechanisms involved. We report that modest changes in both dietary and plasma potassium affect NCC in vivo. Kinase assay studies showed that chloride inhibits WNK4 kinase

activity at lower concentrations than it inhibits activity of WNK1 or WNK3. Also, chloride inhibited WNK4 within the range of distal cell chloride concentration. Mutation of a previously identified WNK chloride-binding motif converted WNK4 effects on SPAK from inhibitory to stimulatory in mammalian cells. Disruption of this motif in WNKs 1, 3, and 4 had different effects on NCC, consistent with the three WNKs having different chloride sensitivities. Thus, potassium effects on NCC are graded within the physiological range, which explains how unique chloride-sensing properties of WNK4 enable it to mediate effects of potassium on NCC in vivo. *Kidney International* advance online publication, 30 September 2015; doi:10.1038/ki.2015.289.

Theodoroff, S. M., & Folmer, R. L. (2015). Hearing loss associated with long-term exposure to high-speed dental handpieces. *General Dentistry*, 63(3), 71-76.

The purpose of this study was to record and compare audiometric pure tone thresholds of dental clinicians (DCs), dental professionals (DPs), and dental students (DSs); determine the percentage of these groups who use hearing protection devices while at work in the clinic; and measure the sound intensities generated by a few representative highspeed handpieces while they are being used on patients. Participants included DCs who regularly used these handpieces (n = 16), DPs who did not use these handpieces (n = 13), and DSs (n = 8). A questionnaire was used to collect demographic information, assess occupational and recreational noise exposure, and note the level of hearing protection used. A sound level meter was used to measure the sound intensity generated by dental instruments near a clinician's ear. Results showed that DCs who regularly used high-speed handpieces had worse hearing than did members of the other study groups. These results indicate that the implementation of protective strategies should help to reduce the prevalence of occupational hearing loss among DCs.

Thornburg, K. L., & Marshall, N. (2015). The placenta is the center of the chronic disease universe. *American Journal of Obstetrics and Gynecology*, 213(4 Suppl), S14-20.

Thosar, S. S., Wiggins, C. C., Shea, S. A., & Wallace, J. P. (2015). Brachial artery endothelial function is stable across the morning in young men. *Cardiovascular Ultrasound*, 13(1), 42-015-0036-1. BACKGROUND: The morning hours are associated with increased cardiovascular (CV) risk, and vascular endothelial function (VEF) is a strong predictor of CV disease. A diurnal rhythm in VEF

has been established but the morning variation in VEF is not well-documented. Thus, we tested if VEF is impaired across the vulnerable morning period. METHODS: After overnight fasts, eight healthy men (age 26.3 +/- 3 yr) underwent assessments of VEF under standardized testing conditions every 2 h from 0700 to 1300 h on two separate days. VEF was estimated following 5 min brachial artery occlusions by hyperemic flow-mediated dilation (FMD). RESULTS: There was no significant change in FMD or hyperemic shear stimulus across the 6 h vulnerable period on either day, despite changes in physical activity and meals across these periods. CONCLUSION: In this healthy group of young men, VEF is stable across the vulnerable morning period when typical behaviors occurred (breakfast and physical activity). Future research should focus on the roles of sleep, physical inactivity during sleep and endogenous circadian rhythm in VEF.

Tiffany Win, T., Ambale Venkatesh, B., Volpe, G. J., Mewton, N., Rizzi, P., Sharma, R. K., et al.

(2015). Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: The PRIMERI study. *Heart Rhythm : The Official Journal of the Heart Rhythm Society*, 12(1), 155-162.

BACKGROUND: Abnormal P-terminal force in lead V1 (PTFV1) is associated with an increased risk of heart failure, stroke, atrial fibrillation, and death. OBJECTIVE: Our goal was to explore associations of left ventricular (LV) diffuse fibrosis with left atrial (LA) function and electrocardiographic (ECG) measures of LA electrical activity. METHODS: Patients without atrial fibrillation (n = 91; mean age 59.5 years; 61.5% men; 65.9% white) with structural heart disease (spatial QRS-T angle  $\geq 105$  degrees and/or Selvester QRS score  $\geq 5$  on ECG) but LV ejection fraction  $> 35\%$  underwent clinical evaluation, cardiac magnetic resonance, and resting ECG. LA function indices were obtained by multimodality tissue tracking using 2- and 4-chamber long-axis images. T1 mapping and late gadolinium enhancement were used to assess diffuse LV fibrosis and presence of scar. P-prime in V1 amplitude (PPaV1) and duration (PPdV1), averaged P-wave-duration, PR interval, and P-wave axis were automatically measured using 12 SLTM algorithm. PTFV1 was calculated as a product of PPaV1 and PPdV1. RESULTS: In linear regression after adjustment for demographic characteristics, body mass index, maximum LA volume index, presence of scar, and LV mass index, each decile increase in LV interstitial fibrosis was associated with 0.76 mV\*ms increase in negative abnormal PTFV1 (95% confidence interval [CI] -1.42 to -

0.09; P = .025), 15.3 ms prolongation of PPdV1 (95% CI 6.9 to 23.8; P = .001) and 5.4 ms prolongation of averaged P-duration (95% CI 0.9-10.0; P = .020). LV fibrosis did not affect LA function. PPaV1 and PTFV1 were associated with an increase in LA volumes and decrease in LA emptying fraction and LA reservoir function. CONCLUSION: LV interstitial fibrosis is associated with abnormal PTFV1, prolonged PPdV1, and P-duration, but does not affect LA function.

Tomita, T. (2015). Apoptosis in pancreatic  $\beta$ -cells in type 1 and type 2 diabetes. (pp. 845-872) Springer Netherlands.

Apoptosis plays an important role in the pathophysiology of both type 1 and type 2 diabetes. In type 1 diabetes,  $\beta$ -cell death by apoptosis following autoimmune insulinitis causes an absolute insulin deficiency triggered by an extrinsic receptor-mediated pathway, which activates a cascade of caspase family reaction. The etiology of type 2 diabetes is multifactorial, including obesity-associated insulin resistance, defective insulin secretion, and loss of  $\beta$ -cell mass through  $\beta$ -cell apoptosis.  $\beta$ -cell apoptosis is mediated through a myriad of caspase family cascade machinery in both type 1 and type 2 diabetes. The glucose-induced insulin secretion is the principle pathophysiology of diabetes and insufficient insulin secretion results in chronic hyperglycemia and diabetes. Recently, hyperglycemia-induced  $\beta$ -cell apoptosis has been extensively studied with regard to the balance of pro-apoptotic genes (Bad, Bid, and Bik) and the antiapoptotic Bcl family toward apoptosis in in vitro isolated islets. Apoptosis can only occur when the concentration of pro-apoptotic Bcl-2 exceeds that of antiapoptotic proteins at the mitochondrial membrane of the intrinsic pathway. © Springer Science+Business Media Dordrecht 2010, 2015.

Torby, A., Turner, M. B., Kinzie, J. M., & Usher, C. (2015). What we talk about when we talk about supervision: The clear and the confusing in graduate psychiatric education. *Journal of the American Psychoanalytic Association*, 63(5), NP7-NP12.

Tsukamoto, H., Kubo, Y., Farrens, D. L., Koyanagi, M., Terakita, A., & Furutani, Y. (2015). Retinal attachment instability is diversified among mammalian melanopsins. *The Journal of Biological Chemistry*,

Melanopsins play a key role in non-visual photoreception in mammals. Their close phylogenetic relationship to the photopigments in invertebrate visual cells suggests they have evolved to

acquire molecular characteristics that are more suited for their non-visual functions. Here we set out to identify such characteristics, by comparing the molecular properties of mammalian melanopsin to those of invertebrate melanopsin and visual pigment. Our data show that the Schiff base linking the chromophore retinal to the protein is more susceptible to spontaneous cleavage in mammalian melanopsins. We also find this stability is highly diversified between mammalian species, being particularly unstable for human melanopsin. Through mutagenesis analyses, we find that this diversified stability is mainly due to parallel amino acid substitutions in extra-cellular regions. We propose that the different stability of the retinal attachment in melanopsins may contribute to functional tuning of non-visual photoreception in mammals.

Turner, H. N. (2015). It takes a village. *Pain Management Nursing*, 16(5), 633.

Uhrenholt, L., Freeman, M. D., Webb, A. L., Pedersen, M., & Boel, L. W. (2015). Fatal subarachnoid hemorrhage associated with internal carotid artery dissection resulting from whiplash trauma. *Forensic Science, Medicine, and Pathology*,

Spinal injury following inertial loading of the head and neck (whiplash) is a common sequel of low speed traffic crashes. A variety of non-musculoskeletal injuries have been described in association with injury to the spine following whiplash trauma, including traumatic brain injury, vestibular derangement, and cranial nerve injury, among others. Vascular injuries in the head and neck have, however, only rarely been described. We present the case of a middle-aged male who sustained an ultimately fatal injury that resulted from injury to the internal carotid artery (ICA) and intracerebral vascular structures following a hard braking maneuver, with no direct head- or neck contact with the vehicular interior. Based on this unusual mechanism of injury we reviewed hospital data from the United States nationwide inpatient database (NIS) to assess the frequency of similar injuries reportedly resulting from traffic crashes. The post-mortem examination revealed a left internal carotid artery dissection associated with subarachnoid hemorrhage (SAH). Based on the close temporal association, the absent prior history, and the plausibility of the injury mechanism, the injury was attributed to the braking maneuver. An analysis of NIS data demonstrated that the prevalence of subarachnoid hemorrhage is significantly higher when there is a traumatic etiology, and higher yet when the trauma is a

traffic crash (odds ratio 3.3 and 4.3, respectively). The presented case, together with the hospital inpatient data analysis, indicate that although SAH in combination with ICA dissection is relatively rare, it is substantially more probable following a traffic crash. In a clinical or forensic setting the inference that magnitude of a trauma was low should not serve as a basis for either excluding a cervical artery dissection from a differential diagnosis, or for excluding the trauma as a cause of a diagnosed dissection. This case report illustrates a rare fatal outcome of inertial load to the head and neck induced by a sudden braking event in a commonly experienced non-collision traffic incident. The likely mechanism of injury resulted from interaction between the occupant and the 3-point seat belt. These findings indicate that ICA dissections are substantially more likely to be associated with SAH following head and neck trauma, regardless of the magnitude of the traumatic event or whether an impact was involved.

Ummadi, J. G., Joshi, V. S., Gupta, P. R., Indra, A. K., & Koley, D. (2015). Single-cell migration as studied by scanning electrochemical microscopy. *Analytical Methods*, 7(20), 8826-8831.

Scanning electrochemical microscopy (SECM) was used to study the migration of single live head and neck cancer cells (SCC25). The newly developed graphite paste ultramicroelectrode (UME) showed significantly less fouling in comparison to a 10  $\mu\text{m}$  Pt-UME and thus could be used to monitor and track the migration pattern of a single cell. We also used SECM probe scan curves to measure the morphology (height and diameter) of a single live cancer cell during cellular migration and determined these dimensions to be  $11 \pm 4 \mu\text{m}$  and  $40 \pm 10 \mu\text{m}$ , respectively. The migration study revealed that cells within the same cell line had a heterogeneous migration pattern (migration and stationary) with an estimated migration speed of  $8 \pm 3 \mu\text{m h}^{-1}$ . However, serum-starved synchronized cells of the same line were found to have a non-heterogeneous cellular migration pattern with a speed of  $9 \pm 3 \mu\text{m h}^{-1}$ . Thus, this non-invasive SECM-based technique could potentially be expanded to other cell lines to study cellular biomechanics for an improved understanding of the structure-function relationship at the level of a single cell. © 2015 The Royal Society of Chemistry.

Urbini, M., Astolfi, A., Indio, V., Heinrich, M. C., Corless, C. L., Nannini, M., et al. (2015). SDHC methylation in gastrointestinal stromal tumors (GIST): A case report. *BMC Medical Genetics*,

16(1), 87-015-0233-7.

**BACKGROUND:** Gastrointestinal stromal tumors (GIST) recently have been recognized as a genetically and biologically heterogeneous disease. In addition to KIT or PDGFRA mutated GIST, mutational inactivation of succinate dehydrogenase (SDH) subunits has been detected in the KIT/PDGFRA wild-type subgroup, referred to as SDH deficient (dSDH). Even though most dSDH GIST harbor mutations in SDHx subunit genes, some are SDHx wild type. Epigenetic regulation by DNA methylation of CpG islands recently has been found to be an alternative mechanism underlying the lack of SDH complex in GIST. **CASE PRESENTATION:** We report a particular case of dSDH GIST, previously analyzed with microarrays and next-generation sequencing, for which no molecular pathogenetic events have been identified. Gene expression analysis showed remarkable down-modulation of SDHC mRNA with respect to all other GIST samples, both SDHA-mutant and KIT/PDGFRA-mutant GIST. By a bisulfite methylation assay targeted to 2 SDHC CpG islands, we detected hypermethylation of the SDHC promoter. **CONCLUSION:** Herein we report an additional case of dSDH GIST without SDHx mutation but harboring hypermethylation in the SDHC promoter, thus confirming the complexity of the molecular background of this subtype of GIST.

Valdivieso, M., Corn, B. W., Dancey, J. E., Wickerham, D. L., Horvath, L. E., Perez, E. A., et al.

(2015). The globalization of cooperative groups. *Seminars in Oncology*, 42(5), 693-712.

The National Cancer Institute (NCI)-supported adult cooperative oncology research groups (now officially Network groups) have a longstanding history of participating in international collaborations throughout the world. Most frequently, the US-based cooperative groups work reciprocally with the Canadian national adult cancer clinical trial group, NCIC CTG (previously the National Cancer Institute of Canada Clinical Trials Group). Thus, Canada is the largest contributor to cooperative groups based in the United States, and vice versa. Although international collaborations have many benefits, they are most frequently utilized to enhance patient accrual to large phase III trials originating in the United States or Canada. Within the cooperative group setting, adequate attention has not been given to the study of cancers that are unique to countries outside the United States and Canada, such as those frequently associated with infections in Latin America, Asia, and Africa. Global collaborations are limited by a number of

barriers, some of which are unique to the countries involved, while others are related to financial support and to US policies that restrict drug distribution outside the United States. This article serves to detail the cooperative group experience in international research and describe how international collaboration in cancer clinical trials is a promising and important area that requires greater consideration in the future.

Vetto, J. T. (2015). Editorial: Colorectal cancer screening education in medically vulnerable populations: The role of the journal of cancer education. *Journal of Cancer Education : The Official Journal of the American Association for Cancer Education*, 30(4), 611-613.

Villasana, L. E., Kim, K. N., Westbrook, G. L., & Schnell, E. (2015). Functional integration of adult-born hippocampal neurons after traumatic brain injury(1,2,3). *Eneuro*, 2(5), 10.1523/ENEURO.0056-15.2015. eCollection 2015 Sep.

Traumatic brain injury (TBI) increases hippocampal neurogenesis, which may contribute to cognitive recovery after injury. However, it is unknown whether TBI-induced adult-born neurons mature normally and functionally integrate into the hippocampal network. We assessed the generation, morphology, and synaptic integration of new hippocampal neurons after a controlled cortical impact (CCI) injury model of TBI. To label TBI-induced newborn neurons, we used 2-month-old POMC-EGFP mice, which transiently and specifically express EGFP in immature hippocampal neurons, and doublecortin-CreER(T2) transgenic mice crossed with Rosa26-CAG-tdTomato reporter mice, to permanently pulse-label a cohort of adult-born hippocampal neurons. TBI increased the generation, outward migration, and dendritic complexity of neurons born during post-traumatic neurogenesis. Cells born after TBI had profound alterations in their dendritic structure, with increased dendritic branching proximal to the soma and widely splayed dendritic branches. These changes were apparent during early dendritic outgrowth and persisted as these cells matured. Whole-cell recordings from neurons generated during post-traumatic neurogenesis demonstrate that they are excitable and functionally integrate into the hippocampal circuit. However, despite their dramatic morphologic abnormalities, we found no differences in the rate of their electrophysiological maturation, or their overall degree of synaptic integration when compared to age-matched adult-born cells from sham mice. Our results suggest that cells

born after TBI participate in information processing, and receive an apparently normal balance of excitatory and inhibitory inputs. However, TBI-induced changes in their anatomic localization and dendritic projection patterns could result in maladaptive network properties.

Wang, K., Kelley, M. H., Wu, W. W., Adelman, J. P., & Maylie, J. (2015). Apamin boosting of synaptic potentials in CaV2.3 R-type Ca<sup>2+</sup> channel null mice. *PLoS One*, *10*(9), e0139332.

SK2- and KV4.2-containing K<sup>+</sup> channels modulate evoked synaptic potentials in CA1 pyramidal neurons. Each is coupled to a distinct Ca<sup>2+</sup> source that provides Ca<sup>2+</sup>-dependent feedback regulation to limit AMPA receptor (AMPA)- and NMDA receptor (NMDAR)-mediated postsynaptic depolarization. SK2-containing channels are activated by Ca<sup>2+</sup> entry through NMDARs, whereas KV4.2-containing channel availability is increased by Ca<sup>2+</sup> entry through SNX-482 (SNX) sensitive CaV2.3 R-type Ca<sup>2+</sup> channels. Recent studies have challenged the functional coupling between NMDARs and SK2-containing channels, suggesting that synaptic SK2-containing channels are instead activated by Ca<sup>2+</sup> entry through R-type Ca<sup>2+</sup> channels. Furthermore, SNX has been implicated to have off target effects, which would challenge the proposed coupling between R-type Ca<sup>2+</sup> channels and KV4.2-containing K<sup>+</sup> channels. To reconcile these conflicting results, we evaluated the effect of SK channel blocker apamin and R-type Ca<sup>2+</sup> channel blocker SNX on evoked excitatory postsynaptic potentials (EPSPs) in CA1 pyramidal neurons from CaV2.3 null mice. The results show that in the absence of CaV2.3 channels, apamin application still boosted EPSPs. The boosting effect of CaV2.3 channel blockers on EPSPs observed in neurons from wild type mice was not observed in neurons from CaV2.3 null mice. These data are consistent with a model in which SK2-containing channels are functionally coupled to NMDARs and KV4.2-containing channels to CaV2.3 channels to provide negative feedback regulation of EPSPs in the spines of CA1 pyramidal neurons.

Ward, A. R., Alarcon, G., Nigg, J. T., & Musser, E. D. (2015). Erratum to: Variation in parasympathetic dysregulation moderates short-term memory problems in childhood attention-deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology*, *43*(8), 1585-015-0083-y.

White, H., Khan, K., Lau, C., Leung, H., Montgomery, D., & Rohlman, D. S. (2015). Identifying health and safety concerns in southeast Asian immigrant nail salon workers. *Archives of Environmental*

*and Occupational Health, 70(4), 196-203.*

Nail salon workers are exposed to a variety of toxic chemicals at levels that remain unreported and have undetermined health consequences. The objective of the study was to gather information about the hazards in nail salons along with safety practices and health concerns of nail salon workers. A survey was conducted on 65 nail salon workers who were immigrants from Southeast Asia in Oregon, USA. More than 20% of the participants reported nose irritation and allergies as the most common health problems. Rare and no use of gloves and mask were reported among 72% and 32% of the participants, respectively. A significantly higher number of participants with "fair" or "poor" self-reported general health condition was found among the workers who applied acrylic nails compared with those who were not involved in this application. Findings of the study emphasize the need for more research to determine the relationship between chemical exposures in nail salons and health outcomes. © 2015 Copyright © Taylor & Francis Group, LLC.

Williams, P., & Chien, J. (2015). Miranda considerations in juvenile defendants. *Journal of the American Academy of Psychiatry and the Law, 43(3), 394-396.*

Williamson, S. S., Gorman, P. N., & Jimison, H. B. (2014). A mobile/web app for long distance caregivers of older adults: Functional requirements and design implications from a user centered design process. *AMIA ...Annual Symposium Proceedings / AMIA Symposium. AMIA Symposium, 2014, 1960-1969.*

Recent trends of population aging and globalization have required an increasing number of individuals to act as long distance caregivers (LDCs) to aging family members. Information technology solutions may ease the burden placed on LDCs by providing remote monitoring, easier access to information and enhanced communication. While some technology tools have been introduced, the information and technology needs of LDCs in particular are not well understood. Consequently, a needs assessment was performed by using video conferencing software to conduct semi-structured interviews with 10 LDCs. Interviews were enriched through the use of stimulus materials that included the demonstration of a prototype LDC health management web/mobile app. Responses were recorded, transcribed and then analyzed. Subjects indicated

that information regarding medication regimens and adherence, calendaring, and cognitive health were most needed. Participants also described needs for video calling, activity data regarding sleep and physical exercise, asynchronous communication, photo sharing, journaling, access to online health resources, real-time monitoring, an overall summary of health, and feedback/suggestions to help them improve as caregivers. In addition, all respondents estimated their usage of a LDC health management website would be at least once per week, with half indicating a desire to access the website from a smartphone. These findings are being used to inform the design of a LDC health management website to promote the meaningful involvement of distant family members in the care of older adults.

Xie, F., Li, B. X., Alkayed, N. J., & Xiao, X. (2015). Synthesis of 14,15-EET from arachidonic acid using urea-hydrogen peroxide as the oxidant. *Synthetic Communications*, 45(1), 105-110.

14,15- Epoxyeicosatrienoic acid (14,15-EET) is an endogenous bioactive lipid with pharmacological benefits in multiple cardiovascular diseases. We describe here a practical synthesis of 14,15-EET from arachidonic acid using urea-hydrogen peroxide (UHP) as the oxidant.

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Yarris, L. M., Miller Juve, A., Coates, W. C., Fisher, J., Heitz, C., Shayne, P., et al. (2015). Critical appraisal of emergency medicine education research: The best publications of 2014. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*,

OBJECTIVES: The objective was to critically appraise and highlight rigorous education research study articles published in 2014 whose outcomes advance the science of emergency medicine (EM) education. METHODS: A search of the English language literature in 2014 querying Education Resources Information Center (ERIC), PsychINFO, PubMed, and Scopus identified 243 EM-related articles using either quantitative (hypothesis-testing or observational investigations of educational interventions) or qualitative (exploring important phenomena in EM education) methods. Two reviewers independently screened all of the publications using previously established exclusion criteria. Six reviewers then independently scored the 25 selected publications using either a qualitative or a quantitative scoring system. Each scoring system consisted of nine criteria. Selected criteria were based on accepted educational review literature

and chosen a priori. Both scoring systems use parallel scoring metrics and have been used previously within this annual review. RESULTS: Twenty-five medical education research papers (22 quantitative, three qualitative) met the criteria for inclusion and were reviewed. Five quantitative and two qualitative studies were ranked most highly by the reviewers as exemplary and are summarized in this article. CONCLUSIONS: This annual critical appraisal series highlights seven excellent EM education research studies, meeting a priori criteria and published in 2014. Methodologic strengths in the 2014 papers are noted, and current trends in medical education research in EM are discussed.

Young, J. H., Logan, B. R., Wu, J., Wingard, J. R., Weisdorf, D. J., Mudrick, C., et al. (2015).

Infections after transplantation of bone marrow or peripheral blood stem cells from unrelated donors. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,

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,  $P = .013$ . 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 ( $P = .003$ ). 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 = .027). 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.

Yuen, K. C., Frystyk, J., Rhoads, S. A., & Bidlingmaier, M. (2015). Pegvisomant-primed glucagon stimulation test in assessing GH reserve and GH/IGF kinetics in adults suspected of GH deficiency. *Pituitary*,

PURPOSE: The accuracy of the glucagon stimulation test (GST) in diagnosing adult GH deficiency (GHD) has recently been questioned. Because pegvisomant (PegV) increases endogenous GH secretion, we hypothesized that priming PegV to the GST (PegV-GST) 72 h beforehand would improve the diagnostic accuracy of this test. This pilot study aimed to prospectively compare PegV-GST to two other diagnostic tests for adult GHD. METHODS: Adults suspected of GHD underwent PegV-GST, GST and insulin tolerance test (ITT) in random order. Growth hormone levels (measured by a PegV insensitive assay) during PegV-GST, GST and ITT were compared, and acute effects of PegV on GH/IGF kinetics were assessed. RESULTS: Ten subjects with hypothalamic-pituitary disease and 1-4 pituitary hormone deficiencies were studied. Basal and peak GH levels with the PegV-GST were comparable to those of the GST and ITT. The five subjects that failed the GST and ITT were the same subjects that failed the PegV-GST, using the peak GH cutpoint of <3 ng/mL for this test. After PegV priming, basal GH and GH binding protein (GHBP) increased (both P < 0.01) and total IGF-I and bioactive IGF decreased (both P < 0.05), whereas IGF-II and IGFBPs -1, -2 and -3 were unchanged compared to pre-PegV priming. Serum PegV levels correlated positively with basal GH, peak GH, IGFBP-1 and IGFBP-2 levels, and negatively with Deltabioactive IGF and DeltaGHBP (all P < 0.05). CONCLUSION: Single dose PegV administration in adults suspected of GHD increased basal GH and GHBP, with concomitant rapid

fall in IGF-I levels and bioactive IGF. PegV priming did not appear to improve the diagnostic accuracy of the GST. Further studies involving larger subject numbers are needed to verify the clinical utility of PegV-GST in evaluating adult GHD.

Zhang, X., Iverson, S. M., Tan, O., & Huang, D. (2015). Effect of signal intensity on measurement of ganglion cell complex and retinal nerve fiber layer scans in fourier-domain optical coherence tomography. *Translational Vision Science & Technology*, 4(5), 7.

**PURPOSE:** We determined the effect of Fourier-domain optical coherence tomography (OCT) signal strength index (SSI) and cropping on retinal nerve fiber layer (RNFL) and macular ganglion cell complex (GCC) scan repeatability and measurement thickness. **METHODS:** Eyes were enrolled in the longitudinal Advanced Imaging for Glaucoma Study. At each visit, three repeat scans from the optic nerve head and macular protocols were obtained. Each measurement was associated with an SSI value from 0 to 100. Measurements with similar SSI scores were grouped to calculate repeatability defined as pooled standard deviation. Within-visit analysis was used to determine how measured thickness changed in relation to change in SSI level. **RESULTS:** The study included 1130 eyes of 569 patients. Cropped images yielded significantly worse repeatability and they were excluded from subsequent analyses. The within-visit repeatability for RNFL and GCC measurements were significantly better with higher signal strength, and optimal cutoffs were SSI  $\geq 37$  and  $\geq 44$ , respectively. The coefficient of variation was  $\leq 37$  and  $\leq 44$ . For scans above the cutoff SSI, higher SSI's were correlated with thicker RNFL among normal (slope = 0.056  $\mu\text{m}/\text{SSI unit}$ ,  $P < 0.001$ ) eyes and glaucoma suspect and perimetric glaucoma (GSPPG) eyes (slope = 0.060  $\mu\text{m}/\text{SSI unit}$ ,  $P < 0.001$ ), but not for perimetric glaucoma (PG) eyes. No significant correlation was found for GCC. **CONCLUSION:** Repeatability of RNFL and GCC thickness measurements may be improved by excluding images with cropped anatomic features and weak signal strength below recommended SSI cutoffs. **TRANSLATIONAL RELEVANCE:** Measurement precision and image quality of inner eye structure by advanced imaging modality are important for clinical diagnosis and tracking of glaucoma disease.

Zhou, P., Liu, J., Merritt, J., & Qi, F. (2015). A YadA-like autotransporter, Hag1 in *veillonella atypica* is a multivalent hemagglutinin involved in adherence to oral streptococci, *porphyromonas gingivalis*,

and human oral buccal cells. *Molecular Oral Microbiology*, 30(4), 269-279.

Dental biofilm development is a sequential process, and adherence between microbes and the salivary pellicle (adhesion) as well as among different microbes (co-adhesion or coaggregation) plays a critical role in building a biofilm community. The *Veillonella* species are among the most predominant species in the oral cavity and coaggregate with many initial, early, middle, and late colonizers. Similar to oral fusobacteria, they are also considered bridging species in biofilm development. However, the mechanism of this ability has yet to be reported, due to the previous lack of a genetic transformation system in the entire genus. In this study, we used our recently discovered transformable *Veillonella* strain, *Veillonella atypica* OK5, to probe the mechanism of coaggregation between *Veillonella* species and other oral bacteria. By insertional inactivation of all eight putative hemagglutinin genes, we identified one gene, *hag1*, which is involved in *V. atypica* coaggregation with the initial colonizers *Streptococcus gordonii*, *Streptococcus oralis* and *Streptococcus cristatus*, and the periodontal pathogen *Porphyromonas gingivalis*. The *hag1* mutant also abolished adherence to human buccal cells. Inhibition assays using various chemical or physiological treatments suggest different mechanisms being involved in coaggregation with different partners. The entire *hag1* gene was sequenced and shown to be the largest known bacterial hemagglutinin gene. © 2015 John Wiley & Sons A/S.

Zindler, J. D., Thomas, C. R., Jr, Hahn, S. M., Hoffmann, A. L., Troost, E. G., & Lambin, P. (2015).

Increasing the therapeutic ratio of stereotactic ablative radiotherapy by individualized isotoxic dose prescription. *Journal of the National Cancer Institute*, 108(2), 10.1093/jnci/djv305. Print 2016 Feb.

To obtain a favorable tradeoff between treatment benefits and morbidity ("therapeutic ratio"), radiotherapy (RT) dose is prescribed according to the tumor volume, with the goal of controlling the disease while respecting normal tissue tolerance levels. We propose a new paradigm for tumor dose prescription in stereotactic ablative radiotherapy (SABR) based on organ-at-risk (OAR) tolerance levels called isotoxic dose prescription (IDP), which is derived from experiences and limitations of conventionally fractionated radiotherapy. With IDP, the radiation dose is prescribed based on the predefined level of normal tissue complication probability of a nearby dose-limiting OAR at a prespecified dose-volume constraint. Simultaneously, the prescribed total

tumor dose (TTD) is maximized to the technically highest achievable level in order to increase the local tumor control probability (TCP). IDP is especially relevant for tumors located at eloquent locations or for large tumors in which severe toxicity has been described. IDP will result in a lower RT dose or a treatment scheduled with more fractions if the OAR tolerance level is exceeded, and potential dose escalation occurs when the OAR tolerance level allows it and when it is expected to be beneficial (if TCP < 90%). For patients with small tumors at noneloquent sites, the current SABR dose prescription already results in high rates of local control at low toxicity rates. In this review, the concept of IDP is described in the context of SABR.

Zuloaga, D. G., Iancu, O. D., Weber, S., Etzel, D., Marzulla, T., Stewart, B., et al. (2015). Enhanced functional connectivity involving the ventromedial hypothalamus following methamphetamine exposure. *Frontiers in Neuroscience*, 9, 326.

Methamphetamine (MA) consumption causes disruption of many biological rhythms including the sleep-wake cycle. This circadian effect is seen shortly following MA exposure and later in life following developmental MA exposure. MA phase shifts, entrains the circadian clock and can also alter the entraining effect of light by currently unknown mechanisms. We analyzed and compared immunoreactivity of the immediate early gene c-Fos, a marker of neuronal activity, to assess neuronal activation 2 h following MA exposure in the light and dark phases. We used network analyses of correlation patterns derived from global brain immunoreactivity patterns of c-Fos, to infer functional connectivity between brain regions. There were five distinct patterns of neuronal activation. In several brain areas, neuronal activation following exposure to MA was stronger in the light than the dark phase, highlighting the importance of considering circadian periods of increased effects of MA in defining experimental conditions and understanding the mechanisms underlying detrimental effects of MA exposure to brain function. Functional connectivity between the ventromedial hypothalamus (VMH) and other brain areas, including the paraventricular nucleus of the hypothalamus and basolateral and medial amygdala, was enhanced following MA exposure, suggesting a role for the VMH in the effects of MA on the brain.