

## References

- Ahmad, F. I., Gerecci, D., Gonzalez, J. D., Peck, J. J., & Wax, M. K. (2015). The role of postoperative hematoma on free flap compromise. *The Laryngoscope*,  
OBJECTIVES/HYPOTHESIS: Hematomas may develop in the postoperative setting after free tissue transfer. When hematomas occur, they can exert pressure on surrounding tissues. Their effect on the vascular pedicle of a free flap is unknown. We describe our incidence of hematoma in free flaps and outcomes when the flap is compromised. STUDY DESIGN: Retrospective chart review of 1,883 free flaps performed between July 1998 and June 2014 at a tertiary referral center. METHODS: Patients with free flap compromise due to hematoma were identified. Etiology, demographic data, and outcomes were evaluated. RESULTS: Eighty-eight (4.7%) patients developed hematomas. Twenty (22.7%) of those had flap compromise. Twelve compromises (60%) showed evidence of pedicle thrombosis. The salvage rate was 75% versus 54% in 79 flaps with compromise from other causes ( $P = .12$ ). Mean time to detection of the hematoma was 35.3 hours in salvaged flaps compared to 91.6 hours in unsalvageable flaps ( $P = .057$ ). Time to operating room (OR) from detection was 2.8 hours in salvageable flaps compared to 12.4 hours in nonsalvageable flaps ( $P = .053$ ). The salvage rate for flaps that returned to the OR in <5 hours was 93.3% compared to 20% ( $P = .0049$ ) for those that did not. Vascular thrombosis reduced salvage rate to 58.3% from 100% ( $P = .002$ ) when there was no thrombosis. CONCLUSIONS: In our series hematomas developed rarely. When they did, 23% went on to develop flap compromise. Prompt recognition and re-exploration allowed for a high salvage rate. Vessel thrombosis predicted inability to salvage the flap. LEVEL OF EVIDENCE: 4 *Laryngoscope*, 2015.
- Ahn, J., Marrero, J., & Reddy, R. K. (2015). Response to zanini et al. *American Journal of Gastroenterology*, 110(4), 600.
- Alarcon, G., Cservenka, A., Rudolph, M. D., Fair, D. A., & Nagel, B. J. (2015). Developmental sex differences in resting state functional connectivity of amygdala sub-regions. *Neuroimage*,  
During adolescence, considerable social and biological changes occur that interact with functional brain maturation, some of which are sex-specific. The amygdala is one brain area that has displayed sexual dimorphism, specifically in socio-affective (superficial amygdala [SFA]), stress

(centromedial amygdala [CMA]), and learning and memory (basolateral amygdala [BLA]) processing. The amygdala has also been implicated in mood and anxiety disorders which also display sex-specific features, most prominently observed during adolescence. Using functional magnetic resonance imaging (fMRI), the present study examined the interaction of age and sex on resting state functional connectivity (RSFC) of amygdala sub-regions, BLA and SFA, in a sample of healthy adolescents between the ages 10 and 16years (n=122, 71 boys). Whole-brain, voxel-wise partial correlation analyses were conducted to determine RSFC of bilateral BLA and SFA seed regions, created using the Eickhoff-Zilles maximum probability maps based on cytoarchitectonic mapping and FMRIB's Integrated Registration and Segmentation Tool (FIRST). Monte Carlo simulation was implemented to correct for multiple comparisons (threshold of 53 contiguous voxels with a z-value  $\geq 2.25$ ). Results indicated that with increasing age, there was a corresponding decrease in RSFC between both amygdala sub-regions and parieto-occipital cortices, with a concurrent increase in RSFC with medial prefrontal cortex (mPFC). Specifically, boys and girls demonstrated increased coupling of mPFC and left and right SFA with age, respectively; however, neither sex showed increased connectivity between mPFC and BLA, which could indicate relative immaturity of fronto-limbic networks that is similar across sex. A dissociation in connectivity between BLA- and SFA-parieto-occipital RSFC emerged, in which girls had weaker negative RSFC between SFA and parieto-occipital regions and boys had weaker negative RSFC of BLA and parieto-occipital regions with increased age, both standing in contrast to adult patterns of amygdala sub-regional RSFC. The present findings suggest relative immaturity of amygdala sub-regional RSFC with parieto-occipital cortices during adolescence, with unique patterns in both sexes that may support memory and socio-affective processing in boys and girls, respectively. Understanding the underlying normative functional architecture of brain networks associated with the amygdala during adolescence may better inform future research of the neural features associated with increased risk for internalizing psychopathology.

Amling, C. (2015). Managing bone health in men with metastatic prostate cancer: Bone health preservation is critical for improving quality, quantity of life in these patients. *Urology Times*, 43(4)

Andrew Harris, W., Spencer, P., Winthrop, K., & Kravitz, J. (2014). Training mid- to late-career health professionals for clinical work in low-income regions abroad. *Journal of Continuing Education in the Health Professions*, 34(3), 179-185.

Introduction: Oregon Health & Science University (OHSU) Global Health Center has developed a unique training program-Professionals' Training in Global Health (PTGH)-for mid- and late-career health professionals wanting to perform clinical services overseas in low-income countries.

Methods: A multidisciplinary, multifaceted, structured curriculum underpins the clinical retraining, with classes aimed to be practical for clinical settings in resource-poor regions of the world.

Preceptorships in family medicine and emergency medicine offer specialists the opportunity to observe primary care physicians one-on-one. In addition, PTGH trainees volunteer at free medical clinics where they work under the guidance and supervision of a family physician. For those individuals who live at some distance from Portland, Oregon, the course offers live

videoconferencing, as well as archived streaming for later review. Results: As of November 2013, 79 health professionals have completed the course, with 45 graduates having subsequently volunteered on one or more overseas medical missions, for a total of 109 medical service visits to 36 countries. Pre- and post-course testing shows improvements in clinical skills and knowledge base.

Discussion: Professionals' Training in Global Health has a 6-year record of interprofessional training and service both overseas and at home. The course has trained physicians, nurses, nurse practitioners, physician assistants, midwives, paramedics and other health professionals. © 2014 The Alliance for Continuing Education in the Health Professions, the Society for Academic Continuing Medical Education, and the Council on Continuing Medical Education, Association for Hospital Medical Education.

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, allyl (cyclohexyloxy)acetate, CAS registry number 68901-15-5. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association*,

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, allyl phenylacetate, CAS registry number 1797-74-6. *Food and*

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

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, alpha-irone, CAS registry number 79-69-6. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, borneol, CAS registry number 507-70-0. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, ethyl anthranilate, CAS registry number 87-25-2. *Food and Chemical Toxicology : An International Journal Published for the British Industrial Biological Research Association,*

Api, A. M., Belsito, D., Bhatia, S., Bruze, M., Calow, P., Dagli, M. L., et al. (2015). RIFM fragrance ingredient safety assessment, l-borneol, CAS registry number 464-45-9. *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 assessment. Repeated Dose Toxicity was determined using read across analog to have the most conservative systemic exposure derived NO[A]EL of 15 mg/kg/day, based on a gavage 13-week subchronic toxicity study conducted in rats, that resulted in a MOE of 3061, considering 100% absorption from skin contact and inhalation. A MOE of >100 is deemed acceptable.

Ash, J. S., Sittig, D. F., McMullen, C. K., Wright, A., Bunce, A., Mohan, V., et al. (2015). Multiple perspectives on clinical decision support: A qualitative study of fifteen clinical and vendor organizations. *BMC Medical Informatics and Decision Making*, 15(1), 35.

BACKGROUND: Computerized clinical decision support (CDS) can help hospitals to improve healthcare. However, CDS can be problematic. The purpose of this study was to discover how the views of clinical stakeholders, CDS content vendors, and EHR vendors are alike or different with respect to challenges in the development, management, and use of CDS. METHODS: We conducted ethnographic fieldwork using a Rapid Assessment Process within ten clinical and five health information technology (HIT) vendor organizations. Using an inductive analytical approach, we generated themes from the clinical, content vendor, and electronic health record vendor perspectives and compared them. RESULTS: The groups share views on the importance of appropriate manpower, careful knowledge management, CDS that fits user workflow, the need for communication among the groups, and for mutual strategizing about the future of CDS. However, views of usability, training, metrics, interoperability, product use, and legal issues differed. Recommendations for improvement include increased collaboration to address legal, manpower, and CDS sharing issues. CONCLUSIONS: The three groups share thinking about many aspects of CDS, but views differ in a number of important respects as well. Until these three groups can reach a mutual understanding of the views of the other stakeholders, and work together, CDS will not reach its potential.

Awan, M., Dyer, B. A., Kalpathy-Cramer, J., Bongers, E., Dahele, M., Yang, J., et al. (2015). Auto-segmentation of the brachial plexus assessed with TaCTICS-A software platform for rapid multiple-metric quantitative evaluation of contours. *Acta Oncologica*, 54(4), 556-560.

Balasubramanian, B. A., Cohen, D. J., Davis, M. M., Gunn, R., Dickinson, L. M., Miller, W. L., et al. (2015). Learning evaluation: Blending quality improvement and implementation research methods to study healthcare innovations. *Implementation Science : IS*, 10(1), 31-015-0219-z.

BACKGROUND: In healthcare change interventions, on-the-ground learning about the implementation process is often lost because of a primary focus on outcome improvements. This paper describes the Learning Evaluation, a methodological approach that blends quality

improvement and implementation research methods to study healthcare innovations. METHODS: Learning Evaluation is an approach to multi-organization assessment. Qualitative and quantitative data are collected to conduct real-time assessment of implementation processes while also assessing changes in context, facilitating quality improvement using run charts and audit and feedback, and generating transportable lessons. Five principles are the foundation of this approach: (1) gather data to describe changes made by healthcare organizations and how changes are implemented; (2) collect process and outcome data relevant to healthcare organizations and to the research team; (3) assess multi-level contextual factors that affect implementation, process, outcome, and transportability; (4) assist healthcare organizations in using data for continuous quality improvement; and (5) operationalize common measurement strategies to generate transportable results. RESULTS: Learning Evaluation principles are applied across organizations by the following: (1) establishing a detailed understanding of the baseline implementation plan; (2) identifying target populations and tracking relevant process measures; (3) collecting and analyzing real-time quantitative and qualitative data on important contextual factors; (4) synthesizing data and emerging findings and sharing with stakeholders on an ongoing basis; and (5) harmonizing and fostering learning from process and outcome data. Application to a multi-site program focused on primary care and behavioral health integration shows the feasibility and utility of Learning Evaluation for generating real-time insights into evolving implementation processes. CONCLUSIONS: Learning Evaluation generates systematic and rigorous cross-organizational findings about implementing healthcare innovations while also enhancing organizational capacity and accelerating translation of findings by facilitating continuous learning within individual sites. Researchers evaluating change initiatives and healthcare organizations implementing improvement initiatives may benefit from a Learning Evaluation approach.

Bao, K., Nasr, K. A., Hyun, H., Lee, J. H., Gravier, J., Gibbs, S. L., et al. (2015). Charge and hydrophobicity effects of NIR fluorophores on bone-specific imaging. *Theranostics*, 5(6), 609-617. Recent advances in near-infrared (NIR) fluorescence imaging enabled real-time intraoperative detection of bone metastases, bone growth, and tissue microcalcification. Pamidronate (PAM) has been widely used for this purpose because of its high binding affinity toward bone and

remarkable therapeutic effects. Herein we describe the development of a series of PAM-conjugated NIR fluorophores that varied in net charges and hydrophobicity, and compared their bone targeting efficiency, biodistribution, and blood clearance. Since the targeting moiety, PAM, is highly negatively charged but small, the overall in vivo bone targeting and biodistribution were mediated by the physicochemical properties of conjugated fluorophores.

Beckley, R., & Roark, B. (2013). Pair language models for deriving alternative pronunciations and spellings from pronunciation dictionaries. *2013 Conference on Empirical Methods in Natural Language Processing, EMNLP 2013*, pp. 1584-1589.

Pronunciation dictionaries provide a readily available parallel corpus for learning to transduce between character strings and phoneme strings or vice versa. Translation models can be used to derive character-level paraphrases on either side of this transduction, allowing for the automatic derivation of alternative pronunciations or spellings. We examine finite-state and SMT-based methods for these related tasks, and demonstrate that the tasks have different characteristics - finding alternative spellings is harder than alternative pronunciations and benefits from round-trip algorithms when the other does not. We also show that we can increase accuracy by modeling syllable stress. © 2013 Association for Computational Linguistics.

Belcik, J. T., Davidson, B. P., Foster, T., Qi, Y., Zhao, Y., Peters, D., et al. (2015). Contrast-enhanced ultrasound assessment of impaired adipose tissue and muscle perfusion in insulin-resistant mice. *Circulation. Cardiovascular Imaging*, 8(4), 10.1161/CIRCIMAGING.114.002684.

**BACKGROUND:** In diabetes mellitus, reduced perfusion and capillary surface area in skeletal muscle, which is a major glucose storage site, contribute to abnormal glucose homeostasis. Using contrast-enhanced ultrasound, we investigated whether abdominal adipose tissue perfusion is abnormal in insulin resistance and correlates with glycemic control. **METHODS AND RESULTS:** Contrast-enhanced ultrasound perfusion imaging of abdominal adipose tissue and skeletal muscle was performed in obese insulin resistance (db/db) mice at 11 to 12 or 14 to 16 weeks of age and in control lean mice. Time-intensity data were analyzed to quantify microvascular blood flow (MBF) and capillary blood volume (CBV). Blood glucose response for 1 hour was measured after insulin challenge (1 U/kg, IP). Compared with control mice, db/db mice at 11 to 12 and 14 to 16

weeks had a higher glucose concentration area under the curve after insulin (11.8 $\pm$ 2.8, 20.6 $\pm$ 4.3, and 28.4 $\pm$ 5.9 mg.min/dL [x1000], respectively; P=0.0002) and also had lower adipose MBF (0.094 $\pm$ 0.038, 0.035 $\pm$ 0.010, and 0.023 $\pm$ 0.01 mL/min per gram; P=0.0002) and CBV (1.6 $\pm$ 0.6, 1.0 $\pm$ 0.3, and 0.5 $\pm$ 0.1 mL/100 g; P=0.0017). The glucose area under the curve correlated in a nonlinear fashion with both adipose and skeletal muscle MBF and CBV. There were significant linear correlations between adipose and muscle MBF (r=0.81) and CBV (r=0.66). Adipocyte cell volume on histology was 25-fold higher in 14- to 16-week db/db versus control mice. CONCLUSIONS: Abnormal adipose MBF and CBV in insulin resistance can be detected by contrast-enhanced ultrasound and correlates with the degree of impairment in glucose storage. Abnormalities in adipose tissue and muscle seem to be coupled. Impaired adipose tissue perfusion is in part explained by an increase in adipocyte size without proportional vascular response.

Belcik, J. T., Mott, B. H., Xie, A., Zhao, Y., Kim, S., Lindner, N. J., et al. (2015). Augmentation of limb perfusion and reversal of tissue ischemia produced by ultrasound-mediated microbubble cavitation. *Circulation Cardiovascular Imaging*, 8(4), 10.1161/CIRCIMAGING.114.002979.

BACKGROUND: Ultrasound can increase tissue blood flow, in part, through the intravascular shear produced by oscillatory pressure fluctuations. We hypothesized that ultrasound-mediated increases in perfusion can be augmented by microbubble contrast agents that undergo ultrasound-mediated cavitation and sought to characterize the biological mediators. METHODS AND RESULTS: Contrast ultrasound perfusion imaging of hindlimb skeletal muscle and femoral artery diameter measurement were performed in nonischemic mice after unilateral 10-minute exposure to intermittent ultrasound alone (mechanical index, 0.6 or 1.3) or ultrasound with lipid microbubbles (2x10<sup>8</sup> IV). Studies were also performed after inhibiting shear- or pressure-dependent vasodilator pathways, and in mice with hindlimb ischemia. Ultrasound alone produced a 2-fold increase (P<0.05) in muscle perfusion regardless of ultrasound power. Ultrasound-mediated augmentation in flow was greater with microbubbles (3- and 10-fold higher than control for mechanical index 0.6 and 1.3, respectively; P<0.05), as was femoral artery dilation. Inhibition of endothelial nitric oxide synthase attenuated flow augmentation produced by ultrasound and microbubbles by 70% (P<0.01), whereas inhibition of adenosine-A2a receptors and

epoxyeicosatrienoic acids had minimal effect. Limb nitric oxide production and muscle phospho-endothelial nitric oxide synthase increased in a stepwise fashion by ultrasound and ultrasound with microbubbles. In mice with unilateral hindlimb ischemia (40%-50% reduction in flow), ultrasound (mechanical index, 1.3) with microbubbles increased perfusion by 2-fold to a degree that was greater than the control nonischemic limb. CONCLUSIONS: Increases in muscle blood flow during high-power ultrasound are markedly amplified by the intravascular presence of microbubbles and can reverse tissue ischemia. These effects are most likely mediated by cavitation-related increases in shear and activation of endothelial nitric oxide synthase.

Bennett, C., Moayyedi, P., Corley, D. A., DeCaestecker, J., Falck-Ytter, Y., Falk, G., et al. (2015). BOB CAT: A large-scale review and delphi consensus for management of barrett's esophagus with no dysplasia, indefinite for, or low-grade dysplasia. *The American Journal of Gastroenterology*,  
OBJECTIVES: Barrett's esophagus (BE) is a common premalignant lesion for which surveillance is recommended. This strategy is limited by considerable variations in clinical practice. We conducted an international, multidisciplinary, systematic search and evidence-based review of BE and provided consensus recommendations for clinical use in patients with nondysplastic, indefinite, and low-grade dysplasia (LGD). METHODS: We defined the scope, proposed statements, and searched electronic databases, yielding 20,558 publications that were screened, selected online, and formed the evidence base. We used a Delphi consensus process, with an 80% agreement threshold, using GRADE (Grading of Recommendations Assessment, Development and Evaluation) to categorize the quality of evidence and strength of recommendations. RESULTS: In total, 80% of respondents agreed with 55 of 127 statements in the final voting rounds. Population endoscopic screening is not recommended and screening should target only very high-risk cases of males aged over 60 years with chronic uncontrolled reflux. A new international definition of BE was agreed upon. For any degree of dysplasia, at least two specialist gastrointestinal (GI) pathologists are required. Risk factors for cancer include male gender, length of BE, and central obesity. Endoscopic resection should be used for visible, nodular areas. Surveillance is not recommended for <5 years of life expectancy. Management strategies for indefinite dysplasia (IND) and LGD were identified, including a de-escalation strategy for lower-risk patients and escalation to intervention with follow-up for higher-risk

patients. CONCLUSIONS: In this uniquely large consensus process in gastroenterology, we made key clinical recommendations for the escalation/de-escalation of BE in clinical practice. We made strong recommendations for the prioritization of future research. *Am J Gastroenterol* advance online publication, 14 April 2015; doi:10.1038/ajg.2015.55.

Bentley-Lewis, R., Aguilar, D., Riddle, M. C., Claggett, B., Diaz, R., Dickstein, K., et al. (2015).

Rationale, design, and baseline characteristics in evaluation of LIXisenatide in acute coronary syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo. *American Heart Journal*,

Cardiovascular (CV) disease is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). Furthermore, patients with T2DM and acute coronary syndrome (ACS) have a particularly high risk of CV events. The glucagon-like peptide 1 receptor agonist, lixisenatide, improves glycemia, but its effects on CV events have not been thoroughly evaluated. Methods: ELIXA ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) no. NCT01147250) is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of lixisenatide in patients with T2DM and a recent ACS event. The primary aim is to evaluate the effects of lixisenatide on CV morbidity and mortality in a population at high CV risk. The primary efficacy end point is a composite of time to CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. Data are systematically collected for safety outcomes, including hypoglycemia, pancreatitis, and malignancy. Results: Enrollment began in July 2010 and ended in August 2013; 6,068 patients from 49 countries were randomized. Of these, 69% are men and 75% are white; at baseline, the mean  $\pm$  SD age was  $60.3 \pm 9.7$  years, body mass index was  $30.2 \pm 5.7$  kg/m<sup>2</sup>, and duration of T2DM was  $9.3 \pm 8.2$  years. The qualifying ACS was a myocardial infarction in 83% and unstable angina in 17%. The study will continue until the positive adjudication of the protocol-specified number of primary CV events. Conclusion: ELIXA will be the first trial to report the safety and efficacy of a glucagon-like peptide 1 receptor agonist in people with T2DM and high CV event risk. © 2015.

Bentz, M. R., & Primack, S. L. (2015). Intensive care unit imaging. *Clinics in Chest Medicine*,

Chest radiography serves a crucial role in imaging of the critically ill. It is essential in ensuring

the proper positioning of support and monitoring equipment, and in evaluating for potential complications of this equipment. The radiograph is useful in diagnosing and evaluating the progression of atelectasis, aspiration, pulmonary edema, pneumonia, and pleural fluid collections. Computed tomography can be useful when the clinical and radiologic presentations are discrepant, the patient is not responding to therapy, or in further defining the pattern and distribution of a radiographic abnormality. © 2015 Elsevier Inc.

Berry, P. (2015). Hospice and palliative care: Differences matter. *International Journal of Palliative Nursing, 21*(3), 107.

Bhalla, P., Forrest, G. N., Gershon, M., Zhou, Y., Chen, J., LaRussa, P., et al. (2015). Disseminated, persistent, and fatal infection due to the vaccine strain of varicella-zoster virus in an adult following stem cell transplantation. *Clinical Infectious Diseases, 60*(7), 1068-1074.

Live attenuated varicella vaccine is recommended for healthy individuals who are susceptible to varicella. Although the vaccine is safe, effective, and used worldwide, serious adverse events have been reported, mainly in immunocompromised patients who subsequently recovered. Here, we describe the fatality of an immunocompromised patient who received the varicella vaccine. His medical history provides a cautionary lens through which to view the decision of when vaccination is appropriate. A middle-aged man with non-Hodgkin lymphoma received chemotherapy and a stem cell transplant. He was vaccinated 4 years post-transplantation, despite diagnosis of a new low-grade lymphoma confined to the lymph nodes. Within 3 months of vaccination, he developed recurrent rashes with fever, malaise, weakness, hepatitis, weight loss, and renal failure. The syndrome was eventually determined to be associated with persistent disseminated zoster caused by the vaccine virus. This case illustrates a circumstance when a live viral vaccine should not be used. © The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America.

Bleyer, A., Asselin, B. L., Koontz, S. E., & Hunger, S. P. (2015). Clinical application of asparaginase activity levels following treatment with pegaspargase. *Pediatric Blood and Cancer, 62*(6), 1102-1105.

Asparaginase, an enzyme used to treat acute lymphoblastic leukemia and related forms of

nonHodgkin lymphoma, depletes asparagine, which leads to lymphoblast cell death. Unlike most chemotherapeutic agents, asparaginase is a foreign protein that can result in clinical allergy and/or silent hypersensitivity with production of neutralizing antibodies that inactivate asparaginase. In North America, asparaginase activity levels can now be obtained via a commercially available assay, for therapeutic drug monitoring and investigation of potential allergic reactions. Herein, we provide recommendations and a corresponding algorithm for the clinical application of this assay after treatment with pegaspargase to evaluate suspected hypersensitivity reactions and/or silent inactivation. © 2014 Wiley Periodicals, Inc.

Bleyer, A., Asselin, B. L., Koontz, S. E., & Hunger, S. P. (2015). Reply to: Colon LB, perissinotti A, santarosa M, marini BL. pharmacokinetic and clinical considerations for monitoring asparaginase activity levels during pegaspargase therapy. *Pediatric Blood and Cancer*, 62(6), 1116-1116.

Blouw, B., Patel, M., Iizuka, S., Abdullah, C., You, W. K., Huang, X., et al. (2015). The invadopodia scaffold protein Tks5 is required for the growth of human breast cancer cells in vitro and in vivo. *Plos One*, 10(3)

The ability of cancer cells to invade underlies metastatic progression. One mechanism by which cancer cells can become invasive is through the formation of structures called invadopodia, which are dynamic, actin-rich membrane protrusions that are sites of focal extracellular matrix degradation. While there is a growing consensus that invadopodia are instrumental in tumor metastasis, less is known about whether they are involved in tumor growth, particularly in vivo. The adaptor protein Tks5 is an obligate component of invadopodia, and is linked molecularly to both actin-remodeling proteins and pericellular proteases. Tks5 appears to localize exclusively to invadopodia in cancer cells, and in vitro studies have demonstrated its critical requirement for the invasive nature of these cells, making it an ideal surrogate to investigate the role of invadopodia in vivo. In this study, we examined how Tks5 contributes to human breast cancer progression. We used immunohistochemistry and RNA sequencing data to evaluate Tks5 expression in clinical samples, and we characterized the role of Tks5 in breast cancer progression using RNA interference and orthotopic implantation in SCID-Beige mice. We found that Tks5 is expressed to high levels in approximately 50% of primary invasive breast cancers. Furthermore, high

expression was correlated with poor outcome, particularly in those patients with late relapse of stage I/II disease. Knockdown of Tks5 expression in breast cancer cells resulted in decreased growth, both in 3D in vitro cultures and in vivo. Moreover, our data also suggest that Tks5 is important for the integrity and permeability of the tumor vasculature. Together, this work establishes an important role for Tks5 in tumor growth in vivo, and suggests that invadopodia may play broad roles in tumor progression. © 2015 Blouw et al.

Bohun, C. M., Woods, P., Winter, C., Mitchell, J., McLarry, J., Weiss, J., et al. (2015). Challenges of intra-institutional transfer of care from paediatric to adult congenital cardiology: The need for retention as well as transition. *Cardiology in the Young*, , 1-7.

BACKGROUND: Transferring patients with CHD from paediatric to adult care has been challenging, especially across institutions. Within a single institution, some issues such as provider interaction, information exchange, or administrative directives should not play a significant role, and should favour successful transfer. OBJECTIVE: We studied patients who were eligible for transfer to the adult congenital heart disease service within our institution in order to identify factors associated with successful transfer to adult care providers versus failure to transfer. METHODS: Patients above 18 years of age with CHD who were seen by paediatric cardiologists before January, 2008 were identified through a patient-care database. Records were reviewed to determine follow-up between 2008 and 2011 and to determine whether the patient was seen in the adult congenital cardiology clinic, paediatric cardiology clinic, or had no follow-up, and statistical comparisons were made between groups. RESULTS: After reviewing 916 records, 229 patients were considered eligible for transition to adult congenital cardiology. Of these, 77 (34%) were transferred successfully to adult congenital cardiology, 47 (21%) continued to be seen by paediatric cardiologists, and 105 (46%) were lost to follow-up. Those who transferred successfully differed with regard to complexity of diagnosis, insurance, and whether a formal referral was made by a paediatric care provider. Only a small fraction of the patients who were lost to follow-up could be contacted. CONCLUSION: Within a single institution, with shared information systems, administrations, and care providers, successful transfer from paediatric to adult congenital cardiology was still poor. Efforts for successful retention are just as vital as those for transfer.

Boudreau, E. A., Chen, G., Li, X., & Kroenke, C. D. (2008). Magnetic resonance imaging approaches for studying alcoholism using mouse models. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(3), 247-248.

Mice are one of the most commonly used animal models of alcoholism, and extensive genetic and behavioral data related to alcohol consumption and its consequences in different strains are available. However, only recently have researchers begun to combine magnetic resonance imaging (MRI) technology with other experimental strategies to study the effects of alcohol in mice. This powerful combination enables structural and functional data of alcohol's effects on the brain of living animals to be obtained. This article reviews the challenges associated with the use of these technologies in mice and discusses the application of these advanced technologies to mouse models of alcoholism.

Brinjikji, W., Luetmer, P. H., Comstock, B., Bresnahan, B. W., Chen, L. E., Deyo, R. A., et al. (2015). Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *American Journal of Neuroradiology*, 36(4), 811-816.

**BACKGROUND AND PURPOSE:** Degenerative changes are commonly found in spine imaging but often occur in pain-free individuals as well as those with back pain. We sought to estimate the prevalence, by age, of common degenerative spine conditions by performing a systematic review studying the prevalence of spine degeneration on imaging in asymptomatic individuals.

**MATERIALS AND METHODS:** We performed a systematic review of articles reporting the prevalence of imaging findings (CT or MR imaging) in asymptomatic individuals from published English literature through April 2014. Two reviewers evaluated each manuscript. We selected age groupings by decade (20, 30, 40, 50, 60, 70, 80 years), determining age-specific prevalence estimates. For each imaging finding, we fit a generalized linear mixed-effects model for the age-specific prevalence estimate clustering in the study, adjusting for the midpoint of the reported age interval. **RESULTS:** Thirty-three articles reporting imaging findings for 3110 asymptomatic individuals met our study inclusion criteria. The prevalence of disk degeneration in asymptomatic individuals increased from 37% of 20-year-old individuals to 96% of 80-year-old individuals. Disk bulge prevalence increased from 30% of those 20 years of age to 84% of those 80 years of age. Disk protrusion prevalence increased from 29% of those 20 years of age to 43% of those 80

years of age. The prevalence of annular fissure increased from 19% of those 20 years of age to 29% of those 80 years of age. CONCLUSIONS: Imaging findings of spine degeneration are present in high proportions of asymptomatic individuals, increasing with age. Many imaging-based degenerative features are likely part of normal aging and unassociated with pain. These imaging findings must be interpreted in the context of the patient's clinical condition.

Broberg, C., McLarry, J., Mitchell, J., Winter, C., Doberne, J., Woods, P., et al. (2015). Accuracy of administrative data for detection and categorization of adult congenital heart disease patients from an electronic medical record. *Pediatric Cardiology*, 36(4), 719-725.

Diagnostic codes used in healthcare administration have been employed extensively in clinical research to identify target patient populations, including demonstration of important clinical outcomes among adults with congenital heart disease. However, little is known about the reliability of code-derived data in this context. We sought to determine the accuracy of International Classification of Disease-9th Revision (ICD-9) diagnoses and the reliability of retrieval algorithms in adults with congenital heart disease (ACHD). Pilot testing of a hierarchical algorithm to identify ACHD patients and determine their principle congenital diagnosis was performed. A revised algorithm was then applied retrospectively to a sample of all outpatients seen by providers who see general cardiology and ACHD patients. Using all ICD-9 codes available from any encounter, accuracy for detection and categorization of sub-types were compared to physician chart review. After initial testing on 334 patients, the revised algorithm was applied to 740 patients. The sensitivity and specificity for ACHD patient identification from this specialty clinic population were 99 and 88 %, respectively. Of 411 (56 %) non-ACHD patients, 49 were incorrectly categorized as ACHD by the algorithm. Of ACHD patients, 326 of 329 were correctly identified by diagnostic codes and categorization of ACHD defect sub-type was correct in 263 (80 %). Administrative data can be used for identification of ACHD patients based on ICD-9 codes with excellent sensitivity and reasonable specificity. Accurate categorization that would be utilized for quality indicators by ACHD defect type is less robust. Additional testing should be done using non-referral populations. © 2014, Springer Science+Business Media New York.

Broberg, C. S., & Burchill, L. J. (2015). Myocardial factor revisited: The importance of myocardial fibrosis in adults with congenital heart disease. *International Journal of Cardiology*, 189, 204-210.

Pioneers in congenital heart surgery observed that exercise capacity did not return to normal levels despite successful surgical repair, leading some to cite a "myocardial factor" playing a role. They conjectured that residual alterations in myocardial function would be significant for patients' long-term outlook. In fulfillment of their early observations, today's adult congenital heart disease (ACHD) population shows well-recognized features of heart failure, even among patients without clear residual anatomic or hemodynamic abnormalities, demonstrating the vital role of the myocardium in their morbidity and mortality. Whereas the 'myocardial factor' was an elusive concept in the early history of congenital heart care, we now have imaging techniques to detect and quantify one such factor - myocardial fibrosis. Understanding the importance of myocardial fibrosis as a final common pathway in a variety of congenital lesions provides a framework for both the study and treatment of clinical heart failure in this context. While typical heart failure pharmacology should reduce or attenuate fibrogenesis, efforts to show meaningful improvements with standard pharmacotherapy in ACHD repeatedly fall short. This paper considers the importance of myocardial fibrosis and function, the current body of evidence for myocardial fibrosis in ACHD, and its implications for research and treatment.

Brochhausen, M., Haendel, M., Stoeckert, C., & Zheng, J. (2014). Preface. *CEUR Workshop Proceedings*, 1309, 56.

Burton, G. J., Barker, D. J. P., Moffett, A., & Thornburg, K. (2010). *Introduction* Cambridge University Press.

Developmental programming of the fetus is a phenomenon that has profound implications for the health of individuals and societies. The term describes the process by which gene expression in the fetus is influenced by the intrauterine environment, such that the structure of major organs and the homeostatic points of metabolic and endocrine systems are set for life. Through this mechanism, perturbations in the intrauterine experience that affect development may predispose to a spectrum of adult diseases, depending on the system principally affected. Thus, in a recent review the National Institute of Child Health concluded that 'coronary heart disease, the number

one cause of death among adult men and women, is more closely related to low birth weight than to known behavioural risk factors'. The list of diseases continues to grow, and now also includes diverse metabolic, neoplastic and neurological disorders. This striking effect first came to light through epidemiological studies of men in Hertfordshire, UK, who had died from cardiovascular disease. Through the records maintained by the midwives attending the births of these men it was possible to show that death rates from the disease fell across the normal range of birth weight. In a later study of blood pressure levels among men and women in Preston, UK, it was possible to relate birth weight to the weight of the placenta. People with small placentas and people with large placentas in relation to their birth weights had the highest blood pressure levels. © Cambridge University Press 2011.

Burton, G. J., Barker, D. J. P., Moffett, A., & Thornburg, K. (2010). *The placenta and human developmental programming* Cambridge University Press.

Developmental programming is a rapidly advancing discipline of great importance to basic scientists and health professionals alike. This text integrates, for the first time, contributions from world experts to explore the role of the placenta in developmental programming. The book considers the materno-fetal supply line, and how perturbations of placental development impact on its functional capacity. Chapters examine ways in which environmental, immunological and vascular insults regulate expression of conventional and imprinted genes, along with their impact on placental shape and size, transport, metabolism and endocrine function. Research in animal models is integrated with human clinical and epidemiological data, and questions for future research are identified. Transcripts of discussions between the authors allow readers to engage with controversial issues. Essential reading for researchers in placental biology and developmental programming, as well as specialists and trainees in the wider field of reproductive medicine. © Cambridge University Press 2011.

Bushby, K., Finkel, R., Wong, B., Barohn, R., Campbell, C., Comi, G. P., et al. (2014). Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle and Nerve*, 50(4), 477-487.

Introduction: Dystrophinopathy is a rare, severe muscle disorder, and nonsense mutations are

found in 13% of cases. Ataluren was developed to enable ribosomal readthrough of premature stop codons in nonsense mutation (nm) genetic disorders. Methods: Randomized, double-blind, placebo-controlled study; males  $\geq 5$  years with nm-dystrophinopathy received study drug orally 3 times daily, ataluren 10, 10, 20 mg/kg (N=57); ataluren 20, 20, 40 mg/kg (N=60); or placebo (N=57) for 48 weeks. The primary endpoint was change in 6-Minute Walk Distance (6MWD) at Week 48. Results: Ataluren was generally well tolerated. The primary endpoint favored ataluren 10, 10, 20 mg/kg versus placebo; the week 48 6MWD  $\Delta=31.3$  meters, post hoc  $P=0.056$ . Secondary endpoints (timed function tests) showed meaningful differences between ataluren 10, 10, 20 mg/kg, and placebo. Conclusions: As the first investigational new drug targeting the underlying cause of nm-dystrophinopathy, ataluren offers promise as a treatment for this orphan genetic disorder with high unmet medical need. © 2014 Wiley Periodicals, Inc..

Cahill, K. S., McCormick, P. C., & Levi, A. D. (2015). A comprehensive assessment of the risk of bone morphogenetic protein use in spinal fusion surgery and postoperative cancer diagnosis. *Journal of Neurosurgery.Spine*, , 1-8.

The risk of postoperative cancer following the use of recombinant human bone morphogenetic protein (BMP)-2 in spinal fusion is one potential complication that has received significant interest. Until recently, there has been little clinical evidence to support the assertion of potential cancer induction after BMP use in spinal surgery. This report aims to summarize the findings from clinical data available to date from the Yale University Open Data Access (YODA) project as well as more recently published large database studies regarding the association of BMP use in spinal fusion and the risk of postoperative cancer. A detailed review was based on online databases, primary studies, FDA reports, and bibliographies of key articles for studies that assessed the efficacy and safety of BMP in spinal fusion. In an analysis of the YODA project, one meta-analysis detected a statistically significant increase in cancer occurrence at 24 months but not at 48 months, and the other meta-analysis did not detect a significant increase in postoperative cancer occurrence. Analysis of 3 large health care data sets (Medicare, MarketScan, and PearlDiver) revealed that none were able to detect a significant increase in risk of malignant cancers when BMP was used compared with controls. The potential risk of postoperative cancer formation following the use of BMP in spinal fusion must be interpreted on an individual basis for each

patient by the surgeon. There is no conclusive evidence that application of the common formulations of BMP during spinal surgery results in the formation of cancer locally or at a distant site.

Cain, J. M. (2008). *Ethical issues* Cambridge University Press.

Whenever cases occur, attended with circumstances not heretofore observed, or in which the ordinary modes of practice have been attempted without success, it is for the public good... that new remedies and new methods of chirurgical treatment should be devised. But in the accomplishment of this salutary purpose... the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts. Thomas Percival (1780–1804) *Medical Ethics: or, a Code of Institutes and Precepts Adapted to the Professional Conduct of Physicians and Surgeons* Manchester: S. Russell, 1803, pp. 14–15. The sometimes-conflicting moral obligations that physicians hold to both mother and fetus in obstetrics (termed maternal-fetal conflict) capture the most poignant of ethical quandaries. Fortunately, circumstances in which the pregnant woman makes choices that are not in the best interest of the developing fetus are actually quite rare. Most pregnant women accept remarkable levels of bodily intrusion or invasion, increased costs, and time-consuming medical interventions to ensure the greatest likelihood of successful outcome. For few other situations would it be anticipated that any person should submit to the level of personal discomfort, potential life-threatening intervention, and self-denial that is routinely expected of pregnant women for an entity that is not yet and might never be a person. In this society, an expectation of extraordinary self-sacrifice practiced by most pregnant women is the norm, and pregnant mothers who question this behavior become immediately suspect. © John P. O'Grady 2008 and Cambridge University Press, 2009.

Carney, P. A., Eiff, M. P., Green, L. A., Carraccio, C., Smith, D. G., Pugno, P. A., et al. (2015).

Transforming primary care residency training: A collaborative faculty development initiative among family medicine, internal medicine, and pediatric residencies. *Academic Medicine : Journal of the Association of American Medical Colleges*,

PROBLEM: The scope and scale of developments in health care redesign have not been sufficiently adopted in primary care residency programs. APPROACH: The interdisciplinary

Primary Care Faculty Development Initiative was created to teach faculty how to accelerate revisions in primary care residency training. The program focused on skill development in teamwork, change management, leadership, population management, clinical microsystems, and competency assessment. The 2013 pilot program involved 36 family medicine, internal medicine, and pediatric faculty members from 12 residencies in four locations. OUTCOMES: The percentage of participants rating intention to implement what was learned as "very likely to" or "absolutely will" was 16/32 (50%) for leadership, 24/33 (72.7%) for change management, 23/33 (69.7%) for systems thinking, 25/32 (75.8%) for population management, 28/33 (84.9%) for teamwork, 29/33 (87.8%) for competency assessment, and 30/31 (96.7%) for patient centeredness. Content analysis revealed five key themes: leadership skills are key drivers of change, but program faculty face big challenges in changing culture and engaging stakeholders; access to data from electronic health records for population management is a universal challenge; readiness to change varies among the three disciplines and among residencies within each discipline; focusing on patients and their needs galvanizes collaborative efforts across disciplines and within residencies; and collaboration among disciplines to develop and use shared measures of residency programs and learner outcomes can guide and inspire program changes and urgently needed educational research. NEXT STEPS: Revise and reevaluate this rapidly evolving program toward widespread engagement with family medicine, internal medicine, and pediatric residencies.

Castro, V. M., Minnier, J., Murphy, S. N., Kohane, I., Churchill, S. E., Gainer, V., et al. (2015).

Validation of electronic health record phenotyping of bipolar disorder cases and controls. *The American Journal of Psychiatry*, 172(4), 363-372.

OBJECTIVE: The study was designed to validate use of electronic health records (EHRs) for diagnosing bipolar disorder and classifying control subjects. METHOD: EHR data were obtained from a health care system of more than 4.6 million patients spanning more than 20 years. Experienced clinicians reviewed charts to identify text features and coded data consistent or inconsistent with a diagnosis of bipolar disorder. Natural language processing was used to train a diagnostic algorithm with 95% specificity for classifying bipolar disorder. Filtered coded data were used to derive three additional classification rules for case subjects and one for control subjects.

The positive predictive value (PPV) of EHR-based bipolar disorder and subphenotype diagnoses was calculated against diagnoses from direct semistructured interviews of 190 patients by trained clinicians blind to EHR diagnosis. RESULTS: The PPV of bipolar disorder defined by natural language processing was 0.85. Coded classification based on strict filtering achieved a value of 0.79, but classifications based on less stringent criteria performed less well. No EHR-classified control subject received a diagnosis of bipolar disorder on the basis of direct interview (PPV=1.0). For most subphenotypes, values exceeded 0.80. The EHR-based classifications were used to accrue 4,500 bipolar disorder cases and 5,000 controls for genetic analyses. CONCLUSIONS: Semiautomated mining of EHRs can be used to ascertain bipolar disorder patients and control subjects with high specificity and predictive value compared with diagnostic interviews. EHRs provide a powerful resource for high-throughput phenotyping for genetic and clinical research.

Catalano, O. A., Nicolai, E., Rosen, B. R., Luongo, A., Catalano, M., Iannace, C., et al. (2015).

Comparison of CE-FDG-PET/CT with CE-FDG-PET/MR in the evaluation of osseous metastases in breast cancer patients. *British Journal of Cancer*, 112(9), 1452-1460.

BACKGROUND: Despite improvements in treatments, metastatic breast cancer remains difficult to cure. Bones constitute the most common site of first-time recurrence, occurring in 40-75% of cases. Therefore, evaluation for possible osseous metastases is crucial. Technetium 99 ((99)Tc) bone scintigraphy and fluorodexosyglucose (FDG) positron emission tomography (PET)-computed tomography (PET-CT) are the most commonly used techniques to assess osseous metastasis. PET magnetic resonance (PET-MR) imaging is an innovative technique still under investigation. We compared the capability of PET-MR to that of same-day PET-CT to assess osseous metastases in patients with breast cancer. METHODS: One hundred and nine patients with breast cancer, who underwent same-day contrast enhanced (CE)-PET-CT and CE-PET-MR, were evaluated. CE-PET-CT and CE-PET-MR studies were interpreted by consensus by a radiologist and a nuclear medicine physician. Correlations with prior imaging and follow-up studies were used as the reference standard. Binomial confidence intervals and a chi(2) test were used for categorical data, and paired t-test was used for the SUVmax data; a non-informative prior Bayesian approach was used to estimate and compare the specificities. RESULTS: Osseous metastases affected 25 out 109 patients. Metastases were demonstrated by CE-PET-CT in 22 out

of 25 patients (88%+/-7%), and by CE-PET-MR in 25 out of 25 patients (100%). CE-PET-CT revealed 90 osseous metastases and CE-PET-MR revealed 141 osseous metastases ( $P < 0.001$ ). The estimated sensitivity of CE-PET-CT and CE-PET-MR were 0.8519 and 0.9630, respectively. The estimated specificity for CE-FDG-PET-MR was 0.9884. The specificity of CE-PET-CT cannot be determined from patient-level data, because CE-PET-CT yielded a false-positive lesion in a patient who also had other, true metastases. CONCLUSIONS: CE-PET-MR detected a higher number of osseous metastases than did same-day CE-PET-CT, and was positive for 12% of the patients deemed osseous metastasis-negative on the basis of CE-PET-CT.

Cathcart-Rake, E., Corless, C., Sauer, D., & Lopez-Chavez, A. (2015). Elderly former smoker with HRAS mutant non-small-cell lung cancer. *Journal of Thoracic Oncology*, 9(10), e75-e78.

Caughey, A. B. (2015). The safe prevention of the primary cesarean delivery in the united states: Why and how? *Clinical Obstetrics and Gynecology*,

The cesarean delivery rate in the United States has risen to epidemic proportions such that 1 in 3 women deliver by cesarean. This rise, a more than 50% increase from 1995 to 2010, was not accompanied by any clear evidence of reductions in neonatal morbidity or mortality. This dramatic rise led several organizations to come together to develop approaches to reducing the cesarean delivery rate in a safe, evidence-based approach. Such approaches include increased patience during the labor and delivery process, both the first and second stage of labor, thoughtful use of fetal heart rate monitoring, prudent use of induction of labor, and maintaining obstetric skills in the management of twin gestations, breech presentations, and fetal malposition. With these approaches, there is hope that there will be a reduction in the rate of cesarean delivery and improvement in the overall quality of care for pregnant women.

Caughey, A. B. (2015). Should pregnancies be induced for impending macrosomia? *Lancet*,

Cetas, J. S., McFarlane, R., Kronfeld, K., Smitasin, P., Liu, J. J., & Raskin, J. S. (2015). Brainstem opioidergic system is involved in early response to experimental SAH. *Translational Stroke Research*, 6(2), 140-147.

Subarachnoid hemorrhage (SAH) is a form of stroke with high rates of mortality and permanent

disability for patients who survive the initial event. Previous research has focused on delayed cerebral vasospasm of large conduit arteries as the cause of poor long-term outcomes after SAH. New evidence suggests that acute failure to restore cerebral blood flow (CBF) after SAH may be setting the stage for delayed ischemic neurological deficits. Our lab previously demonstrated that the rostral ventromedial medulla (RVM), an autonomic and sensorimotor integration center, is important for maintaining CBF after experimental SAH. In this study, we have demonstrated that ablation of  $\mu$ -opioid receptor containing cells with dermorphin conjugates in the RVM results in a high mortality rate after experimental SAH and, in survivors, causes a dramatic decrease in CBF. Further, locally blocking the  $\mu$ -opioid receptor with the antagonist naltrexone attenuated the reduction in CBF secondary to experimental SAH. Saturating  $\mu$ -opioid receptors with the agonist [d-Ala(2),NMe-Phe(4),Gly-ol(5)]-enkephalin (DAMGO) had no effect. Taken together, these results suggest that SAH activates opioidergic signaling in the RVM with a resultant reduction in CBF. Further, cells in the RVM that contain  $\mu$ -opioid receptors are important for survival after acute SAH. We propose that failure of the RVM  $\mu$ -opioid receptor cells to initiate the compensatory CBF response sets the stage for acute and delayed ischemic injury following SAH.

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Chang, B. H., Johnson, K., LaTocha, D., Rowley, J. S., Bryant, J., Burke, R., et al. (2015). YM155 potently kills acute lymphoblastic leukemia cells through activation of the DNA damage pathway. *Journal of Hematology & Oncology*, 8(1), 39-015-0132-6.

BACKGROUND: Novel-targeted therapies are in rapid development for the treatment of acute lymphoblastic leukemia (ALL) to overcome resistance and decrease toxicity. Survivin, a member of the inhibitor of apoptosis gene family and chromosome passenger complex, is critical in a variety of human cancers, including ALL. A well-established suppressor of survivin has been the small molecule, YM155. Reports are identifying other mechanisms of action for YM155. Therefore, we sought to investigate the mode of action and role of YM155 for therapeutic use in the context of ALL. METHODS: Primary ALL samples and ALL cell lines were interrogated with YM155 to identify drug sensitivity. Ph(+)-ALL harboring the BCR-ABL1 oncogene were tested for any interaction with YM155 and the multi-kinase inhibitor dasatinib. Representative ALL cell lines were tested to identify the response to YM155 using standard biochemical assays as well as RNA

expression and phosphorylation arrays. RESULTS: ALL samples exhibited significant sensitivity to YM155, and an additive response was observed with dasatinib in the setting of Ph(+)ALL. ALL cells were more sensitive to YM155 during S phase during DNA replication. YM155 activates the DNA damage pathway leading to phosphorylation of Chk2 and H2AX. Interestingly, screening of primary patient samples identified unique and exquisite YM155 sensitivity in some but not all ALL specimens. CONCLUSION: These results are the first to have screened a large number of primary patient leukemic samples to identify individual variations of response to YM155. Our studies further support that YM155 in ALL induces DNA damage leading to S phase arrest. Finally, only subsets of ALL have exquisite sensitivity to YM155 presumably through both suppression of survivin expression and activation of the DNA damage pathway underscoring its potential for therapeutic development.

Chang, Y. H., Korkola, J., Amin, D. N., Moasser, M. M., Carmena, J. M., Gray, J. W., et al. (2015).

Disentangling multidimensional spatio-temporal data into their common and aberrant responses. *PloS One*, 10(4), e0121607.

With the advent of high-throughput measurement techniques, scientists and engineers are starting to grapple with massive data sets and encountering challenges with how to organize, process and extract information into meaningful structures. Multidimensional spatio-temporal biological data sets such as time series gene expression with various perturbations over different cell lines, or neural spike trains across many experimental trials, have the potential to acquire insight about the dynamic behavior of the system. For this potential to be realized, we need a suitable representation to understand the data. A general question is how to organize the observed data into meaningful structures and how to find an appropriate similarity measure. A natural way of viewing these complex high dimensional data sets is to examine and analyze the large-scale features and then to focus on the interesting details. Since the wide range of experiments and unknown complexity of the underlying system contribute to the heterogeneity of biological data, we develop a new method by proposing an extension of Robust Principal Component Analysis (RPCA), which models common variations across multiple experiments as the lowrank component and anomalies across these experiments as the sparse component. We show that the proposed method is able to find distinct subtypes and classify data sets in a robust

way without any prior knowledge by separating these common responses and abnormal responses. Thus, the proposed method provides us a new representation of these data sets which has the potential to help users acquire new insight from data.

Chao, B., Li, B. X., & Xiao, X. (2015). The chemistry and pharmacology of privileged pyrroloquinazolines. *Medchemcomm*, 6(4), 510-520.

The advent of next-generation sequencing (NGS) technology has plummeted the cost of whole genome sequencing, which has provided a long list of putative drug targets for a variety of diseases ranging from infectious diseases to cancers. The majority of these drug targets are still awaiting high-quality small molecule ligands to validate their therapeutic potential and track their druggability. Screening compound libraries based on privileged scaffolds is an efficient strategy to identify potential ligands to distinct biological targets. 7H-Pyrrolo[3,2-f]quinazoline (PQZ) is a potential privileged heterocyclic scaffold with diverse pharmacological properties. A number of biological targets have been identified for different derivatives of PQZ. This review summarized the synthetic strategies to access the chemical space associated with PQZ and discussed their unique biological profiles. This journal is © The Royal Society of Chemistry.

Chaste, P., Klei, L., Sanders, S. J., Hus, V., Murtha, M. T., Lowe, J. K., et al. (2015). A genome-wide association study of autism using the simons simplex collection: Does reducing phenotypic heterogeneity in autism increase genetic homogeneity? *Biological Psychiatry*, 77(9), 775-784.

Background Phenotypic heterogeneity in autism has long been conjectured to be a major hindrance to the discovery of genetic risk factors, leading to numerous attempts to stratify children based on phenotype to increase power of discovery studies. This approach, however, is based on the hypothesis that phenotypic heterogeneity closely maps to genetic variation, which has not been tested. Our study examines the impact of subphenotyping of a well-characterized autism spectrum disorder (ASD) sample on genetic homogeneity and the ability to discover common genetic variants conferring liability to ASD. Methods Genome-wide genotypic data of 2576 families from the Simons Simplex Collection were analyzed in the overall sample and phenotypic subgroups defined on the basis of diagnosis, IQ, and symptom profiles. We conducted a family-based association study, as well as estimating heritability and evaluating allele scores for

each phenotypic subgroup. Results Association analyses revealed no genome-wide significant association signal. Subphenotyping did not increase power substantially. Moreover, allele scores built from the most associated single nucleotide polymorphisms, based on the odds ratio in the full sample, predicted case status in subsets of the sample equally well and heritability estimates were very similar for all subgroups. Conclusions In genome-wide association analysis of the Simons Simplex Collection sample, reducing phenotypic heterogeneity had at most a modest impact on genetic homogeneity. Our results are based on a relatively small sample, one with greater homogeneity than the entire population; if they apply more broadly, they imply that analysis of subphenotypes is not a productive path forward for discovering genetic risk variants in ASD. © 2015 Society of Biological Psychiatry.

Cheng, S. K., & Dilts, D. M. (2012). *Building expertise in translational processes through partnerships with schools of business*. S. Karger AG.

Translational research in medicine is facing burdens stemming from an increase in the complexity of science, increase in partnerships across national and international collaborations, and reduction in the finite resources to support all research endeavors. Schools of business offer unique perspectives on translational processes because they address global challenges through research and teaching to transform ideas into successful practice-changing innovations. While there are multiple approaches to investigating translational processes using business management tools, this chapter will focus on three representative lenses: (1) process flows for mass customization, (2) knowledge supply chain, and (3) strategic management. Each lens yields the potential to significantly streamline the translational processes in healthcare for efficiency and effectiveness. © 2013 S. Karger AG, Basel.

Cheng, Y. W., & Caughey, A. B. (2015). Second stage of labor. *Clinical Obstetrics and Gynecology*, 58(2), 227-240.

Current American College of Obstetricians and Gynecologists' definition of prolonged second stage diagnoses 10% to 14% of nulliparous and 3% to 3.5% of multiparous women as having a prolonged second stage. The progression of labor in modern obstetrics may have deviated from the current labor norms established in the 1950s, likely due to differences in obstetric population

characteristics and variation in clinical practice. Optimal management of the second stage in women with and without epidural remains debatable. Although prolonged second stage is associated with increased risk of maternal morbidity, conflicting data exist regarding the duration of second stage and associated neonatal morbidity and mortality.

Chiang, W. -, Ko, P. C. -, Chang, A. M., Liu, S. S. -, Wang, H. -, Yang, C. -, et al. (2015).

Predictive performance of universal termination of resuscitation rules in an Asian community: Are they accurate enough? *Emergency Medicine Journal*, 32(4), 318-323.

Introduction: Prehospital termination of resuscitation (TOR) rules have not been widely validated outside of Western countries. This study evaluated the performance of TOR rules in an Asian metropolitan with a mixed-tier emergency medical service (EMS). Methods: We analysed the Utstein registry of adult, non-traumatic out-of-hospital cardiac arrests (OHCAs) in Taipei to test the performance of TOR rules for advanced life support (ALS) or basic life support (BLS) providers. ALS and BLS-TOR rules were tested in OHCAs among three subgroups: (1) resuscitated by ALS, (2) by BLS and (3) by mixed ALS and BLS. Outcome definition was in-hospital death. Sensitivity, specificity, positive predictive value (PPV), negative predictive value and decreased transport rate (DTR) among various provider combinations were calculated. Results: Of the 3489 OHCAs included, 240 were resuscitated by ALS, 1727 by BLS and 1522 by ALS and BLS. Overall survival to hospital discharge was 197 patients (5.6%). Specificity and PPV of ALS-TOR and BLS-TOR for identifying death ranged from 70.7% to 81.8% and 95.1% to 98.1%, respectively. Applying the TOR rules would have a DTR of 34.2-63.9%. BLS rules had better predictive accuracy and DTR than ALS rules among all subgroups. Conclusions: Application of the ALS and BLS TOR rules would have decreased OHCA transported to the hospital, and BLS rules are reasonable as the universal criteria in a mixed-tier EMS. However, 1.9-4.9% of those who survived would be misclassified as non-survivors, raising concern of compromising patient safety for the implementation of the rules. © 2015, BMJ Publishing Group. All rights reserved.

Chiarotto, A., Deyo, R. A., Terwee, C. B., Boers, M., Buchbinder, R., Corbin, T. P., et al. (2015). Core outcome domains for clinical trials in non-specific low back pain. *European Spine Journal*, Purpose: Inconsistent reporting of outcomes in clinical trials of patients with non-specific low

back pain (NSLBP) hinders comparison of findings and the reliability of systematic reviews. A core outcome set (COS) can address this issue as it defines a minimum set of outcomes that should be reported in all clinical trials. In 1998, Deyo et al. recommended a standardized set of outcomes for LBP clinical research. The aim of this study was to update these recommendations by determining which outcome domains should be included in a COS for clinical trials in NSLBP.

Methods: An International Steering Committee established the methodology to develop this COS. The OMERACT Filter 2.0 framework was used to draw a list of potential core domains that were presented in a Delphi study. Researchers, care providers and patients were invited to participate in three Delphi rounds and were asked to judge which domains were core. A priori criteria for consensus were established before each round and were analysed together with arguments provided by panellists on importance, overlap, aggregation and/or addition of potential core domains. The Steering Committee discussed the final results and made final decisions.

Results: A set of 280 experts was invited to participate in the Delphi; response rates in the three rounds were 52, 50 and 45 %. Of 41 potential core domains presented in the first round, 13 had sufficient support to be presented for rating in the third round. Overall consensus was reached for the inclusion of three domains in this COS: 'physical functioning', 'pain intensity' and 'health-related quality of life'. Consensus on 'physical functioning' and 'pain intensity' was consistent across all stakeholders, 'health-related quality of life' was not supported by the patients, and all the other domains were not supported by two or more groups of stakeholders. Weighting all possible argumentations, the Steering Committee decided to include in the COS the three domains that reached overall consensus and the domain 'number of deaths'.

Conclusions: The following outcome domains were included in this updated COS: 'physical functioning', 'pain intensity', 'health-related quality of life' and 'number of deaths'. The next step for the development of this COS will be to determine which measurement instruments best measure these domains. © 2015 The Author(s)

Chiarotto, A., Terwee, C. B., Deyo, R. A., Boers, M., Lin, C. -. C., Buchbinder, R., et al. (2014). A core outcome set for clinical trials on non-specific low back pain: Study protocol for the development of a core domain set. *Trials*, 15(1)

Background: Low back pain (LBP) is one of the most disabling and costly disorders affecting

modern society, and approximately 90% of patients are labelled as having non-specific LBP (NSLBP). Several interventions for patients with NSLBP have been assessed in clinical trials, but heterogeneous reporting of outcomes in these trials has hindered comparison of results and performance of meta-analyses. Moreover, there is a risk of selective outcome reporting bias. To address these issues, the development of a core outcome set (COS) that should be measured in all clinical trials for a specific health condition has been recommended. A standardized set of outcomes for LBP was proposed in 1998, however, with evolution in COS development methodology, new instruments, interventions, and understanding of measurement properties, it is appropriate to update that proposal. This protocol describes the methods used in the initial step in developing a COS for NSLBP, namely, establishing a core domain set that should be measured in all clinical trials. Methods/Design: An International Steering Committee including researchers, clinicians, and patient representatives from four continents was formed to guide the development of this COS. The approach of initiatives like Core Outcome Measures in Effectiveness Trials (COMET) and Outcome Measures in Rheumatology (OMERACT) was followed. Participants were invited to participate in a Delphi study aimed at generating a consensus-based core domain set for NSLBP. A list of potential core domains was drafted and presented to the Delphi participants who were asked to judge which domains were core. Participant suggestions about overlap, aggregation, or addition of potential core domains were addressed during the study. The patients' responses were isolated to assess whether there was substantial disagreement with the rest of the Delphi panel. A priori thresholds for consensus were established before each Delphi round. All participants' responses were analysed from a quantitative and qualitative perspective to ascertain that no substantial discrepancies between the two approaches emerged. Discussion: We present the initial step in developing a COS for NSLBP. The next step will be to determine which measurement instruments adequately cover the domains. © Chiarotto et al.

Childers, R. E., Williams, J. L., & Sonnenberg, A. (2015). Practice patterns of sedation for colonoscopy. *Gastrointestinal Endoscopy*,

BACKGROUND: Sedative and analgesic medications have been used routinely for decades to provide patient comfort, reduce procedure time, and improve examination quality during colonoscopy. OBJECTIVE: To evaluate trends of sedation during colonoscopy in the United States.

SETTING: Endoscopic data repository of U.S. gastroenterology practices (Clinical Outcomes Research Initiative, CORI database from 2000 until 2013). PATIENTS: The study population was made up of patients undergoing a total of 1,385,436 colonoscopies. INTERVENTIONS: Colonoscopy without any intervention or with mucosal biopsy, polypectomy, various means of hemostasis, luminal dilation, stent placement, or ablation. MAIN OUTCOME MEASUREMENTS: Dose of midazolam, diazepam, fentanyl, meperidine, diphenhydramine, promethazine, and propofol used for sedation during colonoscopy. RESULTS: During the past 14 years, midazolam, fentanyl, and propofol have become the most commonly used sedatives for colonoscopy. Except for benzodiazepines, which were dosed higher in women than men, equal doses of sedation were given to female and male patients. White patients were given higher doses than other ethnic groups undergoing sedation for colonoscopy. Except for histamine-1 receptor antagonists, all sedative medications were given at lower doses to patients with increasing age. The dose of sedatives was higher in colonoscopies associated with procedural interventions or of long duration. LIMITATIONS: Potential for incomplete or incorrect documentation in the database. CONCLUSION: The findings reflect on colonoscopy practice in the United States during the last 14 years and provide an incentive for future research on how sex and ethnicity influence sedation practices.

Chiodo, G. T., Tilden, V. P., & Tolle, S. W. (1993). Cross-cultural issues in family violence. *General Dentistry*, 41(6), 516, 518-9.

Choo, E. K. (2008). *Male genitourinary infections* Cambridge University Press.

INTRODUCTION: The male urinary tract is contiguous with the reproductive organs, so infections arising in the urethra, epididymis, testicle and prostate share common symptoms of dysuria, frequency, and urgency. In healthy young or middle-aged men presenting to the acute care setting, these symptoms are unlikely to be caused by simple cystitis and are usually attributable to sexually transmitted disease or prostatitis. URETHRITIS: Epidemiology: Urethritis affects about 4 million males in the United States each year. The peak incidence is in males age 20–24. It is most often a sexually transmitted disease, caused by *Neisseria gonorrhoeae* (gonococcal urethritis) or *Chlamydia trachomatis* (nongonococcal urethritis, NGU). Other nongonococcal

causes include *Ureaplasma urealyticum*, *Mycoplasma hominis*, or *Trichomonas vaginalis* (see Chapter 18, Nonulcerative Sexually Transmitted Diseases). Rare infectious causes of urethritis include lymphogranuloma venereum, herpes genitalis, syphilis, mycobacterium, and adenovirus. Enteric species can cause urethral infection in patients who practice insertive anal intercourse or patients with urethral strictures who develop cystitis. Clinical Features: Male patients with urethritis may present with dysuria, penile discharge, and a history of unprotected sexual contact (Table 20.1). However, up to half of men are asymptomatic and present only because they were referred by a sexual partner who was diagnosed with a sexually transmitted disease (STD). Gonococcal urethritis is more likely to be symptomatic than nongonococcal urethritis. Differential Diagnosis: The differential includes postinstrumentation (traumatic) urethritis, cystitis, pyelonephritis, urethral stricture, and urethral foreign body. © Rachel L. Chin 2008 and Cambridge University Press, 2009.

Clare, M. M., Jimenez, A., & McClendon, J. (2013). *Tomael tiempo: The wisdom of migrant families in consultation* Taylor and Francis.

Clarke, L. E., Warf, B. M., Flake, D. D., Hartman, A. -, Tahan, S., Shea, C. R., et al. (2015). Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma. *Journal of Cutaneous Pathology*,  
Background: Histopathologic examination is sometimes inadequate for accurate and reproducible diagnosis of certain melanocytic neoplasms. As a result, more sophisticated and objective methods have been sought. The goal of this study was to identify a gene expression signature that reliably differentiated benign and malignant melanocytic lesions and evaluate its potential clinical applicability. Herein, we describe the development of a gene expression signature and its clinical validation using multiple independent cohorts of melanocytic lesions representing a broad spectrum of histopathologic subtypes. Methods: Using quantitative reverse-transcription polymerase chain reaction (PCR) on a selected set of 23 differentially expressed genes, and by applying a threshold value and weighting algorithm, we developed a gene expression signature that produced a score that differentiated benign nevi from malignant melanomas. Results: The gene expression signature classified melanocytic lesions as benign or malignant with a sensitivity

of 89% and a specificity of 93% in a training cohort of 464 samples. The signature was validated in an independent clinical cohort of 437 samples, with a sensitivity of 90% and specificity of 91%. Conclusions: The performance, objectivity, reliability and minimal tissue requirements of this test suggest that it could have clinical application as an adjunct to histopathology in the diagnosis of melanocytic neoplasms. © 2015 The Authors.

Coates, C. S., Milikisiyants, S., Chatterjee, R., Whittaker, M. M., Whittaker, J. W., & Lakshmi, K. V. (2015). Two-dimensional HYSCORE spectroscopy of superoxidized manganese catalase: A model for the oxygen-evolving complex of photosystem II. *Journal of Physical Chemistry B*, 119(15), 4905-4916.

The solar water-splitting protein complex, photosystem II (PSII), catalyzes one of the most energetically demanding reactions in Nature by using light energy to drive a catalyst capable of oxidizing water. The water oxidation reaction takes place at the tetra-nuclear manganese calcium-oxo (Mn<sub>4</sub>Ca-oxo) cluster at the heart of the oxygen-evolving complex (OEC) of PSII. Previous studies have determined the magnetic interactions between the paramagnetic Mn<sub>4</sub>Ca-oxo cluster and its environment in the S<sub>2</sub> state of the OEC. The assignments for the electron-nuclear magnetic interactions that were observed in these studies were facilitated by the use of synthetic dimanganese di- $\mu$ -oxo complexes. However, there is an immense need to understand the effects of the protein environment on the coordination geometry of the Mn<sub>4</sub>Ca-oxo cluster in the OEC of PSII. In the present study, we use a proteinaceous model system to examine the protein ligands that are coordinated to the dimanganese catalytic center of manganese catalase from *Lactobacillus plantarum*. We utilize two-dimensional hyperfine sublevel correlation (2D HYSCORE) spectroscopy to detect the weak magnetic interactions of the paramagnetic dinuclear manganese catalytic center of superoxidized manganese catalase with the nitrogen and proton atoms of the surrounding protein environment. We obtain a complete set of hyperfine interaction parameters for the protons of a water molecule that is directly coordinated to the dinuclear manganese center. We also obtain a complete set of hyperfine and quadrupolar interaction parameters for two histidine ligands as well as a coordinated azide ligand, in azide-treated superoxidized manganese catalase. On the basis of the values of the hyperfine interaction parameters of the dimanganese model, manganese catalase, and those of the S<sub>2</sub> state of the

OEC of PSII, for the first time, we discuss the impact of a proteinaceous environment on the coordination geometry of multinuclear manganese clusters. © 2015 American Chemical Society.

Coleman, C. A., & Fromer, A. (2015). A health literacy training intervention for physicians and other health professionals. *Family Medicine, 47*(5), 388-392.

**BACKGROUND AND OBJECTIVES:** Health literacy is a key factor in communication between patients and health care professionals of all kinds. Improving the training of health professionals about patients' health literacy is a national priority that remains understudied. We sought to examine the effects of a health literacy training on physicians and nonphysician health professionals. **METHODS:** We used a pre-/post-intervention self-reported assessment of knowledge, perceived skills, and current and intended behaviors vis-a-vis communicating with patients who have limited health literacy to evaluate the effects of a 3.5-hour health literacy training intervention designed to improve communication with such patients for the entire staff of a single family medicine residency program clinic. **RESULTS:** A total of 58 health professionals participated. Complete data were available for 45 individuals (11 physicians and 34 nonphysicians). Forty-eight percent reported having initially overestimated their pre-training understanding of health literacy issues. Mean ratings significantly improved on all 12 knowledge, perceived skill, and intended behavior items. Results varied by health profession, with physicians reporting less positive change on several items. Among physicians, the training impact varied by years of experience. **CONCLUSIONS:** Health literacy training for health professionals can improve self-perceived knowledge, skills, and intended behaviors, but results may vary between physicians and nonphysician health professionals and by years of experience. More research is needed to identify ideal instructional strategies for teaching health professionals about health literacy.

Cook, V. C., Timock, A. M., Crowe, J. J., Wang, M., & Covell, D. A., Jr. (2015). Accuracy of alveolar bone measurements from cone beam computed tomography acquired using varying settings. *Orthodontics & Craniofacial Research, 18 Suppl 1*, 127-136.

**OBJECTIVES:** To investigate the accuracy and reliability of cone beam computed tomography (CBCT) measurements of buccal alveolar bone height (BBH) and thickness (BBT) using custom

acquisition settings. SETTINGS AND SAMPLE POPULATION: School of Dentistry, Oregon Health & Science University. Twelve embalmed cadavers. MATERIALS AND METHODS: Cadaver heads were imaged by CBCT (i-CAT((R)) 17-19, Imaging Sciences International, Hatfield, PA) using a 'long scan' (LS) setting with 619 projection images, 360 degrees revolution, 26.9 s duration, and 0.2 mm voxel size, and using a 'short scan' (SS) setting with 169 projection images, 180 degrees rotation, 4.8 s duration, and 0.3 mm voxel size. BBH and BBT were measured with 65 teeth, indirectly from CBCT images and directly through dissection. Comparisons were assessed using paired t-tests ( $p \leq 0.05$ ). Level of agreement was assessed by concordance correlation coefficients, Pearson's correlation coefficients, and Bland-Altman plots. RESULTS: Mean differences in measurements compared to direct measurements were as follows, LS 0.17 +/- 0.12 (BBH) and 0.10 +/- 0.07 mm (BBT), and SS 0.41 +/- 0.32 (BBH) and 0.12 +/- 0.11 mm (BBT). No statistical differences were found with any of BBH or BBT measurements. Correlation coefficients and Bland-Altman plots showed agreement was high between direct and indirect measurement methods, although agreement was stronger for measurements of BBH than BBT. CONCLUSIONS: Compared to the LS, the similarity in results with the reduced scan times and hence reduced effective radiation dose, favors use of shorter scans, unless other purposes for higher resolution imaging can be defined.

Cozzoli, D. K., Courson, J., Rostock, C., Campbell, R. R., Wroten, M. G., McGregor, H., et al. (2015).

Protein kinase C epsilon activity in the nucleus accumbens and central nucleus of the amygdala mediates binge alcohol consumption. *Biological Psychiatry*,

BACKGROUND: Protein kinase C epsilon (PKCepsilon) is emerging as a potential target for the development of pharmacotherapies to treat alcohol use disorders, yet little is known regarding how a history of a highly prevalent form of drinking, binge alcohol intake, influences enzyme priming or the functional relevance of kinase activity for excessive alcohol intake. METHODS: Immunoblotting was employed on tissue from subregions of the nucleus accumbens (NAc) and the amygdala to examine both idiopathic and binge drinking-induced changes in constitutive PKCepsilon priming. The functional relevance of PKCepsilon translocation for binge drinking and determination of potential upstream signaling pathways involved were investigated using neuropharmacologic approaches within the context of two distinct binge drinking procedures,

drinking in the dark and scheduled high alcohol consumption. RESULTS: Binge alcohol drinking elevated p(Ser729)-PKCepsilon levels in both the NAc and the central nucleus of the amygdala (CeA). Moreover, immunoblotting studies of selectively bred and transgenic mouse lines revealed a positive correlation between the propensity to binge drink alcohol and constitutive p(Ser729)-PKCepsilon levels in the NAc and CeA. Finally, neuropharmacologic inhibition of PKCepsilon translocation within both regions reduced binge alcohol consumption in a manner requiring intact group 1 metabotropic glutamate receptors, Homer2, phospholipase C, and/or phosphatidylinositol-3 kinase function. CONCLUSIONS: Taken together, these data indicate that PKCepsilon signaling in both the NAc and CeA is a major contributor to binge alcohol drinking and to the genetic propensity to consume excessive amounts of alcohol.

Crabbe, J. C. (2014). *Rodent models of genetic contributions to motivation to abuse alcohol* Springer New York LLC.

Cramer, S. K., Skalet, A., Mansoor, A., Wilson, D. J., & Ng, J. D. (2015). Inflammatory myofibroblastic tumor of the orbit: A case report. *Ophthalmic Plastic and Reconstructive Surgery*, 31(1), e22-e23.

Inflammatory myofibroblastic tumor (IMT) is a neoplasm most commonly found in the abdominal-pelvic region, lung, and retroperitoneum. The tumor tends to affect soft tissues of children and young adults and can locally recur but rarely metastasizes.<sup>1</sup> Histologically, the appearance is one of bland spindle cell proliferation with a prominent, chronic inflammatory infiltrate. This article describes 1 case of IMT found in the orbit that is presented with rapidly progressive painless proptosis. In the authors' review of the literature, they have only found 2 other case reports involving the orbit. © 2014 The American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc.

Cuevas, I., Layman, H., Coussens, L., & Boudreau, N. (2015). Sustained endothelial expression of HoxA5 in vivo impairs pathological angiogenesis and tumor progression. *PLoS One*, 10(3), e0121720.

HoxA5 is expressed in quiescent endothelial cells (EC), but absent in activated angiogenic EC. To examine the efficacy of targeting HoxA5 therapeutically to quell pathologic or tumor

angiogenesis, we generated an inducible, transgenic mouse model of sustained HoxA5 expression in ECs. During pathologic angiogenesis, sustained HoxA5 regulates expression several angiogenic effector molecules, notably increased expression of TSP-2 and reduced expression of VEGF, thus leading to inhibition of pathological angiogenesis in tissues. To evaluate if this impressive reduction of vascularization could also impact tumor angiogenesis, HoxA5 mice were bred with a mouse model of de novo squamous carcinogenesis, e.g., K14-HPV16 mice. Activation of EC-HoxA5 significantly reduced infiltration by mast cells into neoplastic skin, an early hallmark of progression to dysplasia, reduced angiogenic vasculature, and blunted characteristics of tumor progression. To evaluate HoxA5 as a therapeutic, topical application of a HoxA5 transgene onto early neoplastic skin of K14-HPV16 mice similarly resulted in a significant impairment of angiogenic vasculature and progression to dysplasia to a similar extent as observed with genetic delivery of HoxA5. Together these data indicate that HoxA5 represents a novel molecule for restricting pathological and tumorigenic angiogenesis.

Day, L. W., Nazareth, M., Sewell, J. L., Williams, J. L., & Lieberman, D. A. (2015). Practice variation in PEG tube placement: Trends and predictors among providers in the united states.

*Gastrointestinal Endoscopy,*

BACKGROUND: Enteral access placement is performed among a variety of providers and specialties, yet there is a dearth of literature on trends and factors related to enteral access placement in the United States. OBJECTIVE: To examine trends in the incidence of enteral access procedures performed by gastroenterologists in the United States. DESIGN: Retrospective review of upper endoscopic procedures that involved PEG tube placement between 2000 and 2010.

SETTING: Endoscopy sites participating in the Clinical Outcomes Research Initiative (CORI).

PATIENTS: Patients undergoing upper endoscopy. INTERVENTIONS: PEG tube placement. MAIN

OUTCOME MEASUREMENTS: Number of PEG tubes placed. RESULTS: Overall PEG tube placement by a provider from 2000 to 2010 was 1.7% (number of PEG tubes performed/number of upper endoscopies performed), with the majority of them being performed by gastroenterologists. Very young and very old, non-white racial background (Hispanic: odds ratio [OR] 1.21; 95% CI, 1.13-1.28; black: OR 2.24; 95% CI, 2.12-2.36), and men (OR 1.44; 95% CI, 1.39-1.50) were patient characteristics associated with greater PEG tube placement. In terms of practice setting, PEG

tube placement occurred more frequently in community and/or health maintenance organization environments and on the East Coast. With respect to provider characteristics, male providers were less likely than female providers to perform a PEG tube insertion (OR 0.67; 95% CI, 0.64-0.71), and there was a trend that as providers were further out of medical school they were less likely to perform a PEG tube procedure. Interestingly, surgeons (OR 6.69; 95% CI, 6.18-7.24) and other providers (non-pediatric/non-general practice) (OR 3.22; 95% CI, 2.63-3.94) were more likely to perform PEG tube procedures than were gastroenterologists. LIMITATIONS: Participation in CORI is voluntary and may not capture data on non-gastroenterologist providers. CONCLUSION: Significant practice variation was noted in PEG tube placement in the United States with respect to patient and provider characteristics, geographic region, and endoscopy settings.

DeBarros, M., Shawhan, R., Bingham, J., Sokol, K., Izenberg, S., & Martin, M. (2015). Assessing serum hemoglobin levels without venipuncture: Accuracy and reliability of pronto-7 noninvasive spot-check device. *American Journal of Surgery*,  
Background: Hemoglobin is a frequently obtained test in hospital settings. We analyzed accuracy of a noninvasive device compared to standard laboratory analyzers in a variety of settings.  
Methods: A noninvasive hemoglobin monitoring device was analyzed for reliability, correlation, precision, and bias. Hemoglobin levels were obtained from standard laboratory and point-of-care hemoglobin analyzers and compared to noninvasive hemoglobin in inpatient and military field environments. Results: Ninety-seven patients were enrolled. Overall, the noninvasive hemoglobin device had high correlation compared to invasive laboratory values. Stratified by location, the device had high correlation in hospital and low correlation in austere environment. The highest variation in accuracy was seen in the austere environment. Conclusions: Overall, the noninvasive spot-check hemoglobin device is reliable and highly correlates to standard hemoglobin analysis. Use in an austere setting requires further study. © 2015.

Deloughery, T. G., & Beer, T. M. (2015). Bevacizumab and thrombosis: Some answers but questions remain. *Cancer*, *121*(7), 975-977.

Denmark, D. L., Milner, L. C., & Buck, K. J. (2008). Interval-specific congenic animals for high-resolution quantitative trait loci mapping. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(3), 266-269.

Behavioral phenotypes (e.g., drug responses and withdrawal) are typically quantitative traits—characteristics that differ along a spectrum in the extent to which an individual possesses that characteristic. Such traits are determined by multiple genes, as well as by environmental factors and interactions among genes and environmental factors. The chromosomal regions containing these genes are commonly referred to as quantitative trait loci (QTLs). As described in the preceding article by Hitzemann and colleagues (pp. 270- 271), researchers have developed a variety of strategies to attain greater precision when mapping QTLs (Darvasi 1998; Talbot et al. 1999), which is necessary for unbiased genomewide approaches such as QTL mapping to be successful in ultimately identifying which gene(s) underlies a QTL's phenotypic influence. Among these, some approaches are clearly superior for fine mapping QTLs associated with behavioral traits. One such strategy employs specially bred animals known as interval-specific congenics (ISCs) (sometimes called small donor segment congenics). This article introduces the use of these animals in mapping QTLs associated with certain responses to alcohol.

Deodhar, A., Braun, J., Inman, R. D., Van Der Heijde, D., Zhou, Y., Xu, S., et al. (2015). Golimumab administered subcutaneously every 4 weeks in ankylosing spondylitis: 5-year results of the GO-RAISE study. *Annals of the Rheumatic Diseases*, 74(4), 757-761.

Objective: Assess golimumab efficacy/safety through 5 years in patients with active ankylosing spondylitis (AS). Methods: 356 patients with AS were randomly assigned to placebo, golimumab 50 mg or 100 mg every 4 weeks. At week 16, patients with inadequate response early escaped with blinded dose adjustments (placebo to 50 mg, 50 mg to 100 mg). At week 24, all patients receiving placebo crossed over to 50 mg. Blinded active therapy continued through week 104; from week 104 to week 252, the golimumab dose could be adjusted. Intent-to-treat and observed efficacy data were assessed by randomised treatment groups. Results: At week 256, and with >4.5 years of golimumab, overall intent-to-treat Assessment in SpondyloArthritis international Society criteria for 20% improvement (ASAS20) and ASAS40 response rates were 66.0% (235/356) and 57.0% (203/356), respectively; Bath AS Disease Activity Index 50% improvement

response was 55.9% (199/356). Observed response rates among the 255 (72%) patients who continued golimumab through week 252 were consistent, albeit somewhat higher. Among patients who increased golimumab from 50 to 100 mg, 60.6% (20/33) and 44.7% (17/38) achieved ASAS20/ASAS40 responses, respectively, following  $\geq 2$  consecutive doses of golimumab 100 mg. Golimumab safety through week 268 was similar to that through week 24 regardless of dose. Conclusions: Clinical improvements observed in patients treated with golimumab through week 24 were sustained through week 256 (5 years). Long-term golimumab safety is consistent with that of other established tumournecrosis-factor-antagonists.

Dobbertin, K., Horner-Johnson, W., Lee, J. C., & Andresen, E. M. (2015). Subgroup differences in having a usual source of health care among working-age adults with and without disabilities. *Disability and Health Journal*, 8(2), 296-302.

Background Having a usual source of health care is positively associated with regular health maintenance visits and receipt of preventive services. People with disabilities are, overall, more likely than those without disabilities to have a usual source of care (USC). However, the population of people with disabilities is quite heterogenous, and some segments of the population may have less access to a USC than others. Objective To determine whether there are significant subgroup differences in having a USC within the U.S. population of working-age adults with disabilities, and to compare adults with and without disabilities while controlling for other subgroup differences. Methods We analyzed Medical Expenditure Panel Survey annual data files from 2002 to 2008. We performed both bivariate and multivariate logistic regression analyses to examine the relationship of sociodemographic and disability subgroup variables with having a USC. Results Within the disability population, individuals who were younger; male; Black, Hispanic, or other (non-White) race; less educated; of lower income; or uninsured for part or all of the year were significantly less likely to have a USC. These differences mirrored those among adults without disabilities. When controlling for these differences, people with physical, hearing, or multiple disabilities had greater odds of having a USC than people without disabilities, but those with vision or cognitive limitations did not differ significantly from the non-disabled referent group. Conclusions Disparities among people with and without disabilities are similar,

underscoring the need for attention to disparities within the disability population. © 2015 Elsevier Inc.

Dodge, H. H., Katsumata, Y., Zhu, J., Mattek, N., Bowman, M., Gregor, M., et al. (2014).

Characteristics associated with willingness to participate in a randomized controlled behavioral clinical trial using home-based personal computers and a webcam. *Trials*, 15(1)

Background: Trials aimed at preventing cognitive decline through cognitive stimulation among those with normal cognition or mild cognitive impairment are of significant importance in delaying the onset of dementia and reducing dementia prevalence. One challenge in these prevention trials is sample recruitment bias. Those willing to volunteer for these trials could be socially active, in relatively good health, and have high educational levels and cognitive function. These participants' characteristics could reduce the generalizability of study results and, more importantly, mask trial effects. We developed a randomized controlled trial to examine whether conversation-based cognitive stimulation delivered through personal computers, a webcam and the internet would have a positive effect on cognitive function among older adults with normal cognition or mild cognitive impairment. To examine the selectivity of samples, we conducted a mass mail-in survey distribution among community-dwelling older adults, assessing factors associated with a willingness to participate in the trial. Methods: Two thousand mail-in surveys were distributed to retirement communities in order to collect data on demographics, the nature and frequency of social activities, personal computer use and additional health-related variables, and interest in the prevention study. We also asked for their contact information if they were interested in being contacted as potential participants in the trial. Results: Of 1,102 surveys returned (55.1% response rate), 983 surveys had complete data for all the variables of interest. Among them, 309 showed interest in the study and provided their contact information (operationally defined as the committed with interest group), 74 provided contact information without interest in the study (committed without interest group), 66 showed interest, but provided no contact information (interest only group), and 534 showed no interest and provided no contact information (no interest group). Compared with the no interest group, the committed with interest group were more likely to be personal computer users (odds ratio (OR)=2.78), physically active (OR=1.03) and had higher levels of loneliness (OR=1.16). Conclusion:

Increasing potential participants' familiarity with a personal computer and the internet before trial recruitment could increase participation rates and improve the generalizability of future studies of this type. © 2014 Dodge et al.

Duncan, C. N., Majhail, N. S., Brazauskas, R., Wang, Z., Cahn, J. -, Frangoul, H. A., et al. (2015).

Long-term survival and late effects among one-year survivors of second allogeneic hematopoietic cell transplantation for relapsed acute leukemia and myelodysplastic syndromes. *Biology of Blood and Marrow Transplantation*, 21(1), 151-158.

We analyzed the outcomes of patients who survived disease-free for 1 year or more after a second allogeneic hematopoietic cell transplantation (HCT) for relapsed acute leukemia or myelodysplastic syndromes between 1980 and 2009. A total of 1285 patients received a second allogeneic transplant after disease relapse; among these, 325 were relapse free at 1 year after the second HCT. The median time from first to second HCT was 17 and 24 months for children and adults, respectively. A myeloablative preparative regimen was used in the second transplantation in 62% of children and 45% of adult patients. The overall 10-year conditional survival rates after second transplantation in this cohort of patients who had survived disease-free for at least 1 year was 55% in children and 39% in adults. Relapse was the leading cause of mortality (77% and 54% of deaths in children and adults, respectively). In multivariate analyses, only disease status before second HCT was significantly associated with higher risk for overall mortality (hazard ratio, 1.71 for patients with disease not in complete remission before second HCT,  $P < .01$ ). Chronic graft-versus-host disease (GVHD) developed in 43% and 75% of children and adults after second transplantation. Chronic GVHD was the leading cause of nonrelapse mortality, followed by organ failure and infection. The cumulative incidence of developing at least 1 of the studied late effects within 10 years after second HCT was 63% in children and 55% in adults. The most frequent late effects in children were growth disturbance (10-year cumulative incidence, 22%) and cataracts (20%); in adults they were cataracts (20%) and avascular necrosis (13%). Among patients with acute leukemia and myelodysplastic syndromes who receive a second allogeneic HCT for relapse and survive disease free for at least 1 year, many can be expected to survive long term. However, they continue to be at risk for relapse and nonrelapse morbidity and mortality. Novel approaches are needed to minimize relapse risk and

long-term transplantation morbidity in this population. © 2015 American Society for Blood and Marrow Transplantation.

Dupuis, D., Ram, N., Willner, C. J., Karalunas, S., Segalowitz, S. J., & Gatzke-Kopp, L. M. (2015).

Implications of ongoing neural development for the measurement of the error-related negativity in childhood. *Developmental Science*, *18*(3), 452-468.

Event-related potentials (ERPs) have been proposed as biomarkers capable of reflecting individual differences in neural processing not necessarily detectable at the behavioral level. However, the role of ERPs in developmental research could be hampered by current methodological approaches to quantification. ERPs are extracted as an average waveform over many trials; however, actual amplitudes would be misrepresented by an average if there was high trial-to-trial variability in signal latency. Low signal temporal consistency is thought to be a characteristic of immature neural systems, although consistency is not routinely measured in ERP research. The present study examined the differential contributions of signal strength and temporal consistency across trials in the error-related negativity (ERN) in 6-year-old children, as well as the developmental changes that occur in these measures. The 234 children were assessed annually in kindergarten, 1st, and 2nd grade. At all assessments signal strength and temporal consistency were highly correlated with the average ERN amplitude, and were not correlated with each other. Consistent with previous findings, ERN deflections in the averaged waveform increased with age. This was found to be a function of developmental increases in signal temporal consistency, whereas signal strength showed a significant decline across this time period. In addition, average ERN amplitudes showed low-to-moderate stability across the three assessments whereas signal strength was highly stable. In contrast, signal temporal consistency did not evidence rank-order stability across these ages. Signal strength appears to reflect a stable individual trait whereas developmental changes in temporal consistency may be experientially influenced. © 2014 John Wiley & Sons Ltd.

Dutta, G. G., McGlade, K. E., Reisman, D. S., & Scholz, J. P. (2015). Trunk muscle coordination when reaching upward and downward in chronic stroke survivors. *Motor Control*,

This study investigated deficits in trunk muscle modes coordination involved in the stabilization of

the trunk's trajectory for reaching upward and downward beyond functional arm length. Trunk muscle activity from ten stroke survivors (8M, 2F; 64.1+/-10.5 yrs) and nine healthy control (7M, 2F; 59.3+/-9.3 yrs) subjects was analyzed. Coordination of trunk muscle modes to stabilize the trunk trajectory was investigated using the uncontrolled manifold analysis (UCM). The UCM analysis decomposes the variability of muscle modes into good and bad variability. The good variability does not affect the control of trunk motion, whereas the bad variability does. In stroke survivors, deficits in the ability to flexibly combine trunk muscle modes was associated with reduced ability to minimize those combinations of trunk muscle modes that led to an error in trunk trajectory (bad variability), more so for reaching upward. This reduced coordination of trunk muscle modes during reaching was correlated with a clinical measure of trunk impairment.

Eapen, M., Logan, B. R., Appelbaum, F. R., Antin, J. H., Anasetti, C., Couriel, D. R., et al. (2015).

Long-term survival after transplantation of unrelated donor peripheral blood or bone marrow hematopoietic cells for hematologic malignancy. *Biology of Blood and Marrow Transplantation*, 21(1), 55-59.

We sought to determine whether differences in chronic graft-versus-host disease (GVHD) rates would lead to survival differences by comparing 2463 peripheral blood (PB) and 1713 bone marrow (BM) hematopoietic cell transplant recipients. Patients had acute leukemia, chronic myeloid leukemia (CML), or myelodysplastic syndrome, and they received myeloablative conditioning regimens and calcineurin-inhibitor GVHD prophylaxis. There were no significant differences in long-term survival after transplantation of PB and BM, except for patients in first chronic phase CML. For these patients, the 5-year rate of survival was lower after transplantation of PB compared with transplantation of BM (35% versus 56%,  $P = .001$ ). Although mortality risks were higher in patients with chronic GVHD after both PB (hazard ratio [HR], 1.58;  $P < .001$ ) and BM (HR 1.73;  $P < .001$ ) transplantations, its effect on mortality did not differ by graft type ( $P = .42$ ). BM is the preferred graft for first chronic phase CML, whereas as either graft is suitable for other leukemias. © 2015 American Society for Blood and Marrow Transplantation.

Eden, K. B., Perrin, N. A., Hanson, G. C., Messing, J. T., Bloom, T. L., Campbell, J. C., et al. (2015).

Use of online safety decision aid by abused women: Effect on decisional conflict in a randomized

controlled trial. *American Journal of Preventive Medicine*, 48(4), 372-383.

**Background** An Internet safety decision aid was developed to help abused women understand their risk for repeat and near-lethal intimate partner violence, clarify priorities related to safety, and develop an action plan customized to these priorities. **Purpose** To test the effectiveness of a safety decision aid compared with usual safety planning (control) delivered through a secure website, using a multistate RCT design. The paper evaluates the effectiveness of the safety decision aid in reducing decisional conflict after a single use by abused women. **Design** RCT referred to as Internet Resource for Intervention and Safety (IRIS). **Setting/participants** Abused women who spoke English (n=708) were enrolled in a four-state RCT. **Intervention** The intervention was an interactive safety decision aid with personalized safety plan; the control condition was usual safety planning resources. Both were delivered to participants through the secure study website. **Main outcome measures** This paper compares women's decisional conflict about safety: total decisional conflict and the four subscales of this measure (feeling: uninformed, uncertain, unsupported, and unclear about safety priorities) between intervention/control conditions. Data were collected from March 2011 to May 2013 and analyzed from January to March 2014. **Results** Immediately following the first use of the interactive safety decision aid, intervention women had significantly lower total decisional conflict than control women, controlling for baseline value of decisional conflict ( $p=0.002$ , effect size=0.12). After controlling for baseline values, the safety decision aid group had significantly greater reduction in feeling uncertain ( $p=0.006$ , effect size=0.07) and in feeling unsupported ( $p=0.008$ , effect size=0.07) about safety than the usual safety planning group. **Conclusions** Abused women randomized to the safety decision aid reported less decisional conflict about their safety in the abusive intimate relationship after one use compared to women randomized to the usual safety planning condition. © 2015 American Journal of Preventive Medicine.

Elkind, J. A., Lim, M. M., Johnson, B. N., Palmer, C. P., Putnam, B. J., Kirschen, M. P., et al. (2015).

Efficacy, dosage, and duration of action of branched chain amino acid therapy for traumatic brain injury. *Frontiers in Neurology*, 6, 73.

Traumatic brain injury (TBI) results in long-lasting cognitive impairments for which there is currently no accepted treatment. A well-established mouse model of mild to moderate TBI, lateral

fluid percussion injury (FPI), shows changes in network excitability in the hippocampus including a decrease in net synaptic efficacy in area CA1 and an increase in net synaptic efficacy in dentate gyrus. Previous studies identified a novel therapy consisting of branched chain amino acids (BCAAs), which restored normal mouse hippocampal responses and ameliorated cognitive impairment following FPI. However, the optimal BCAA dose and length of treatment needed to improve cognitive recovery is unknown. In the current study, mice underwent FPI then consumed 100 mM BCAA supplemented water ad libitum for 2, 3, 4, 5, and 10 days. BCAA therapy ameliorated cognitive impairment at 5 and 10 days duration. Neither BCAA supplementation at 50 mM nor BCAAs when dosed 5 days on then 5 days off was sufficient to ameliorate cognitive impairment. These results suggest that brain injury causes alterations in hippocampal function, which underlie and contribute to hippocampal cognitive impairment, which are reversible with at least 5 days of BCAA treatment, and that sustaining this effect is dependent on continuous treatment. Our findings have profound implications for the clinical investigation of TBI therapy.

Ellenby, M. S., & Marcin, J. P. (2015). The role of telemedicine in pediatric critical care. *Critical Care Clinics, 31*(2), 275-290.

Telemedicine technologies involve real-time, live, interactive video and audio communication and allow pediatric critical care physicians to have a virtual presence at the bedsides of critically ill children. Telemedicine use is increasing and will be a common in remote emergency departments, inpatient wards, and intensive care units for pediatric care. Hospitals and physicians that use telemedicine technologies provide higher quality of care, are more efficient in resource use with improved cost-effectiveness, and have higher satisfaction among patients, parents, and remote providers. More research will result in improved access to pediatric critical care expertise.

Elliot, D., Rohlman, D., & Parish, M. (2015). Focus groups move online: Feasibility of tumblr use for eHealth curriculum development. *JMIR Research Protocols, 4*(1), e34.

BACKGROUND: Constructing successful online programs requires engaging potential users in development. However, assembling focus groups can be costly and time consuming. OBJECTIVE: The aim of this study is to assess whether Tumblr can be used to prioritize activities for an online

younger worker risk reduction and health promotion program. METHODS: Younger summer parks and recreation employees were encouraged to visit Tumblr using weekly announcements and competitions. Each week, new activities were posted on Tumblr with linked survey questions. Responses were downloaded and analyzed. RESULTS: An average of 36 young workers rated each activity on its likeability and perceived educational value. The method was feasible, efficient, and sustainable across the summer weeks. Ratings indicated significant differences in likeability among activities ( $P < .005$ ). CONCLUSIONS: Tumblr is a means to crowdsource formative feedback on potential curricular components when assembling an online intervention. This paper describes its initial use as well as suggestions for future refinements.

Eskandar, A., Ahmed, A., Daughtey, M., Kenderian, S., Mahdi, F., & Khan, A. (2015). Racial and sex differences in presentation and outcomes of small cell lung cancer in the united states: 1973 to 2010. *Chest*, 147(4), e164-e165.

Faggi, F., Chiarelli, N., Colombi, M., Mitola, S., Ronca, R., Madaro, L., et al. (2015). Cavin-1 and caveolin-1 are both required to support cell proliferation, migration and anchorage-independent cell growth in rhabdomyosarcoma. *Laboratory Investigation; a Journal of Technical Methods and Pathology*,

Rhabdomyosarcoma (RMS) is a childhood soft tissue tumor with broad expression of markers that are typically found in skeletal muscle. Cavin-1 is a recently discovered protein actively cooperating with Caveolin-1 (Cav-1) in the morphogenesis of caveolae and whose role in cancer is drawing increasing attention. Using a combined in silico and in vitro analysis here we show that Cavin-1 is expressed in myogenic RMS tumors as well as in human and primary mouse RMS cultures, exhibiting a broad subcellular localization, ranging from nuclei and cytosol to plasma membrane. In particular, the coexpression and plasma membrane interaction between Cavin-1 and Cav-1 characterized the proliferation of human and mouse RMS cell cultures, while a downregulation of their expression levels was observed during the myogenic differentiation. Knockdown of Cavin-1 or Cav-1 in the human RD and RH30 cells led to impairment of cell proliferation and migration. Moreover, loss of Cavin-1 in RD cells impaired the anchorage-independent cell growth in soft agar. While the loss of Cavin-1 did not affect the Cav-1 protein

levels in RMS cells, Cav-1 overexpression and knockdown triggered a rise or depletion of Cavin-1 protein levels in RD cells, respectively, in turn reflecting on increased or decreased cell proliferation, migration and anchorage-independent cell growth. Collectively, these data indicate that the interaction between Cavin-1 and Cav-1 underlies the cell growth and migration in myogenic tumors. *Laboratory Investigation* advance online publication, 30 March 2015; doi:10.1038/labinvest.2015.45.

Fagin, A. P., Howell, T. H., & Park, S. E. (2015). Impact of the NBDE grading change on postgraduate admissions processes. *Journal of Dental Education*, 79(4), 362-368.

The aim of this study was to assess the effect of discontinuing the reporting of National Board Dental Examination (NBDE) Part I numerical scores on postgraduate program directors' admissions selection processes. This cross-sectional survey-based study collected information about two admissions cycles (2012-13 and 2013-14) from directors of American Dental Education Association Postdoctoral Application Support Service (ADEA PASS(SM)) programs in all postdoctoral training disciplines; the response rate was 54.5%. According to the 2012-13 cycle results, these program directors rated an NBDE Part I score the third most important part of an application, behind grade point average (GPA) and class rank (ranked first and second, respectively). In the 2013-14 cycle, in the absence of an NBDE Part I score, almost all other parts of the application increased in importance for the responding directors, but the relative rank of factors remained almost unchanged. Significantly, 71% of the directors reported that it was now more difficult to select interview candidates, and 76% said they wanted some form of national, numerically scored exam. No significant change was noted between the two years in the number of applications or interviews offered per resident position, although the standard deviation of the number of interviews offered increased in both pediatric dentistry and postdoctoral general dentistry.

Fagley, R. E., Haney, M. F., Beraud, A. S., Comfere, T., Kohl, B. A., Merkel, M. J., et al. (2015).

Critical care basic ultrasound learning goals for american anesthesiology critical care trainees: Recommendations from an expert group. *Anesthesia and Analgesia*, 120(5), 1041-1053.

OBJECTIVE: In this review, we define learning goals and recommend competencies concerning

focused basic critical care ultrasound (CCUS) for critical care specialists in training. DESIGN: The narrative review is, and the recommendations contained herein are, sponsored by the Society of Critical Care Anesthesiologists. Our recommendations are based on a structured literature review by an expert panel of anesthesiology intensivists and cardiologists with formal training in ultrasound. Published descriptions of learning and training routines from anesthesia-critical care and other specialties were identified and considered. Sections were written by groups with special expertise, with dissent included in the text. RESULTS: Learning goals and objectives were identified for achieving competence in the use of CCUS at a specialist level (critical care fellowship training) for diagnosis and monitoring of vital organ dysfunction in the critical care environment. The ultrasound examination was divided into vascular, abdominal, thoracic, and cardiac components. For each component, learning goals and specific skills were presented. Suggestions for teaching and training methods were described. DISCUSSION: Immediate bedside availability of ultrasound resources can dramatically improve the ability of critical care physicians to care for critically ill patients. Anesthesia--critical care medicine training should have definitive expectations and performance standards for basic CCUS interpretation by anesthesiology--critical care specialists. The learning goals in this review reflect current trends in the multispecialty critical care environment where ultrasound-based diagnostic strategies are already frequently applied. These competencies should be formally taught as part of an established anesthesiology-critical care medicine graduate medical education programs.

Feldstein Ewing, S. W., Montanaro, E. A., Gaume, J., Caetano, R., & Bryan, A. D. (2015).

Measurement invariance of alcohol instruments with hispanic youth. *Addictive Behaviors*, 46, 113-120.

INTRODUCTION: Despite their widespread use across clinical and research settings, no study has yet investigated the fit of several standard alcohol measures for Hispanic youth, including those used to assess motivation to change, self-efficacy, peer norms, and problem drinking. This study thus served to address this gap by evaluating measurement invariance with substance-using youth. METHODS: We enrolled a large sample of regular substance-using youth who were involved with the justice system (N=368; 72.9% male; 76.9% Hispanic; M age=16.17years). Similar to the broader Hispanic population of the southwest United States (U.S.), Hispanic youth

in the sample were on average 3.5th generation (with at least 1 foreign-born grand-parent). Following standard administration and scoring procedures, all youth completed measures of motivation to change (e.g., readiness rulers, intentions to change), self-efficacy (e.g., drink refusal in social situations), peer norms (e.g., peer norms for substance use), and problem drinking (e.g., substance use quantity/frequency; Alcohol Use Disorders Identification Test; Rutgers Alcohol Problems Index; Timeline FollowBack). Measurement equivalence was evaluated via multiple group confirmatory factor analysis. RESULTS: Our results indicated that each measure evaluated herein worked equally well for Hispanic and Caucasian youth. We found measurement invariance at every level tested. CONCLUSIONS: This study supports the validity and future use of these important and widely-used alcohol use measures for high-risk substance-using Hispanic youth. Further, given the representativeness of this sample within the southwestern U.S., these results show promise for generalizability to U.S.-born Hispanic youth within this geographic region.

Fennell, L. P., & Butler, R. W. (2008). *Neuropsychological assessment of children with cancer*. Cambridge University Press.

Introduction Neuropsychology, broadly defined, is the study of brain-behavior relationships. The term was coined by William Osler in the early 1900s and gained wider appeal in the 1960s. The field was influenced by pioneers in neuroanatomy, neurology, and physiology, who began to explore the brain's functionality (Broca, 1865; Hughlings-Jackson, 1931; Lashley, 1950; Wernicke, 1874). Modern neuropsychology represents a blend of careful clinical observation grounded in the pioneering work of Alexandr Luria (1973), and a more actuarial approach that utilizes psychometric instruments to describe and quantify an individual's functioning (Halstead, 1947; Reitan, 1974). Neuropsychology has become a science of human behavior as it is influenced by brain functioning and by social, psychological, and cultural contexts. Pediatric neuropsychologists are concerned with developmental issues and take into account the genetic, medical, environmental, behavioral, and sociocultural influences that impact the maturation of a child (Baron, 2004). The human nervous system is never static and development occurs across the lifespan. However, the rapidity of development in childhood and adolescence calls for a specific developmental focus when conducting evaluations with this age group. At birth, infants

have more than 100 billion neurons (Berger, 2005). In the first 2 years of life the brain undergoes a period termed transient exuberance when as many as 15 000 new connections are established per neuron (Thompson, 2000). Following this period of rapid growth, there is a period of rapid elimination of synapses called "pruning" that peaks in adolescence and is variable across different brain regions (Kolb & Wishaw, 2003). © Cambridge University Press 2008 and 2009.

Fine, N. A., Lehfelddt, M., Gross, J. E., Downey, S., Kind, G. M., Duda, G., et al. (2015). SERI surgical scaffold, prospective clinical trial of a silk-derived biological scaffold in two-stage breast reconstruction: 1-year data. *Plastic and Reconstructive Surgery*, 135(2), 339-351.

BACKGROUND: SERI Surgical Scaffold is a long-term bioresorbable silk-derived biological scaffold developed to provide soft-tissue support and repair. METHODS: SURE-001 (ClinicalTrials.gov identification no. NCT01256502) is a prospective, single-arm study in the United States of patients undergoing two-stage, implant-based breast reconstruction using SERI. RESULTS: A total of 139 patients were enrolled and will be followed for 2 years; in this article, the authors report interim data on 71 patients followed for 1 year. Investigator satisfaction scores (mean +/- SD) at 6 and 12 months were 9.2 +/- 0.98 and 9.4 +/- 0.91, respectively (10 = very satisfied). SERI was rated easy/very easy to use in 98 percent or more of cases across five categories in stage I surgery. Patient satisfaction with the treated breast(s) (mean +/- SD) was higher at 6 (4.3 +/- 0.87; 5 = very satisfied) and 12 months (4.5 +/- 0.82) compared with screening (3.6 +/- 1.09;  $p < 0.0001$ ). Key complication rates (per breast) were tissue necrosis (6.7 percent), seroma (5.7 percent), hematoma (4.8 percent), implant loss (3.8 percent), capsular contracture (1.9 percent), and breast infection (1.0 percent). None were attributed to SERI by the investigators. In 13 patients (14 breasts) who underwent unplanned radiation therapy, one complication was reported. CONCLUSIONS: In this interim report, high levels of investigator and patient satisfaction, and ease of use of SERI were reported. Prospectively collected complication rates were similar to those reported in primarily retrospective studies of two-stage, implant-based breast reconstructions using other implantable soft-tissue support materials such as acellular dermal matrices. CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Firestone, K. A., Carson, J. W., Mist, S. D., Carson, K. M., & Jones, K. D. (2014). Interest in yoga among fibromyalgia patients: An international internet survey. *International Journal of Yoga Therapy, 24*, 117-124.

Studies in circumscribed clinical settings have reported the adoption of yoga by many fibromyalgia (FM) patients. However, it is unclear from existing studies which types of yoga practices FM patients are typically engaging in and the extent to which they experience yoga as helpful or not. The purpose of this study was to survey FM patients in many different regions to inquire about their engagement in various yoga practices, the perceived benefits, and the obstacles to further practice. A 13-question Internet survey of persons self-identified as FM patients was conducted among subscribers to 2 electronic newsletters on the topic of FM. Respondents (N = 2543) replied from all 50 U.S. states and also from Canada, Australia, and the United Kingdom, and from more than two dozen other countries. On average, respondents were 57 years of age and 96% were female, with an average time since diagnosis of 13 years. Of these respondents, 79.8% had considered trying yoga and 57.8% had attended 1 yoga class. The respondents' classes typically focused almost exclusively on yoga poses, with minimal training in meditation, breathing techniques, or other practices. The most commonly cited benefits were reduced stiffness, relaxation, and better balance. The most frequently cited obstacles were concerns about the poses being too physically demanding and fear that the poses would cause too much pain. These findings confirm strong interest in yoga across a geographically diverse range of FM patients. However, concerns about yoga-induced pain and yoga poses being too difficult are common reasons that FM patients do not engage in yoga exercises. This study supports the need for yoga programs tailored for FM patients to include modification of poses to minimize aggravating movements and substantive training in meditation and other yoga-based coping methods to minimize pain-related fear.

Flanagan, H. E., Smith, I. M., Vaillancourt, T., Duku, E., Szatmari, P., Bryson, S., et al. (2015).

Stability and change in the cognitive and adaptive behaviour scores of preschoolers with autism spectrum disorder. *Journal of Autism and Developmental Disorders,*

We examined the stability of cognitive and adaptive behaviour standard scores in children with autism spectrum disorder (ASD) between diagnosis and school entry approximately age 6. IQ

increased 18 points in 2-year-olds, 12 points in 3-year-olds, and 9 points in 4-year-olds (N = 281). Adaptive behaviour scores increased 4 points across age groups (N = 289). At school entry, 24 % of children met criteria for intellectual disability (cognitive and adaptive behaviour scores <70). No children with both scores  $\geq 70$  at diagnosis later met criteria for intellectual disability. Outcomes were more variable for children with initial delays in both areas (in 57 %, both scores remained <70). Findings are relevant to clinical decision-making, including specification of intellectual disability in young children with ASD. © 2015 Springer Science+Business Media New York

Franasiak, J. M., Burns, K. A., Slayden, O., Yuan, L., Fritz, M. A., Korach, K. S., et al. (2015).

Endometrial CXCL13 expression is cycle regulated in humans and aberrantly expressed in humans and rhesus macaques with endometriosis. *Reproductive Sciences*, 22(4), 442-451.

C-X-C ligand 13 (CXCL13), a regulator of mucosal immunity, is secreted by human endometrial epithelium and may be involved in embryo implantation. However, cyclic expression of human endometrial CXCL13 in health and disease is not well studied. This study examines cycle stage-specific endometrial CXCL13 expression in normal humans when compared to those with biopsy-confirmed, stage 1 to 4 endometriosis using real-time reverse transcriptase, real-time polymerase chain reaction and immunohistochemistry. Eutopic endometrial CXCL13 expression was also compared between normal, control Rhesus macaques, and macaques with advanced endometriosis. In healthy women, CXCL13 messenger RNA expression was minimal in the proliferative phase and maximal in the secretory phase. However, in the presence of endometriosis, proliferative-phase endometrial expression markedly increased in both humans and rhesus subjects ( $P < .05$ ). The cross-species and cross-stage concordance suggests a pathophysiologic role for CXCL13 in endometriosis and its use as a biomarker for disease. © The Author(s) 2014.

Fraunfelder, F. W. (2014). *Ocular side effects of prescription medications* Wiley Blackwell.

Drug-induced ocular side effects are frequently noted after a drug comes to market. Spontaneous reporting systems can collect data and provide a "signal" that a possible drug-adverse reaction relationship exists. It is many times difficult to collect incidence data and cause-and-effect

analysis because this type of spontaneous reporting system is passive. It relies on the reporting physician or patient to provide information, and data are not collected proactively or in a systematic matter. Still, these signals are many times the first evidence available that an adverse reaction is occurring. There are numerous examples throughout ophthalmology whereby spontaneous reports have revealed real ocular side effects. These include topiramate angle-closure glaucoma, bisphosphonate uveitis and scleritis, retinoid-associated pseudotumor cerebri, niacin-induced cystoid macular edema, intraoperative floppy iris syndrome from alpha antagonists, and many other examples. Also, there is now a useful classification system that helps to divide spontaneous reports into categories based upon the completeness of the information. Certain, probable, possible, unlikely, and unclassifiable are all categories that can be applied. This chapter looks at commonly prescribed medications like sildenafil, tamoxifen, amiodarone, topiramate, bisphosphonates, and others and provides an overview of commonly identified adverse drug reactions. © 2014 by John Wiley & Sons, Ltd. All rights reserved.

Frias, A. E., Schabel, M. C., Roberts, V. H. J., Tudorica, A., Grigsby, P. L., Oh, K. Y., et al. (2015).

Using dynamic contrast-enhanced MRI to quantitatively characterize maternal vascular organization in the primate placenta. *Magnetic Resonance in Medicine*, 73(4), 1570-1578.

**Purpose** The maternal microvasculature of the primate placenta is organized into 10-20 perfusion domains that are functionally optimized to facilitate nutrient exchange to support fetal growth. This study describes a dynamic contrast-enhanced magnetic resonance imaging method for identifying vascular domains and quantifying maternal blood flow in them. **Methods** A rhesus macaque on the 133rd day of pregnancy (G133, term=165 days) underwent Doppler ultrasound procedures, dynamic contrast-enhanced magnetic resonance imaging and Cesarean-section delivery. Serial T1-weighted images acquired throughout intravenous injection of a contrast reagent bolus were analyzed to obtain contrast reagent arrival time maps of the placenta. **Results** Watershed segmentation of the arrival time map identified 16 perfusion domains. The number and location of these domains corresponded to anatomical cotyledonary units observed following delivery. Analysis of the contrast reagent wave front through each perfusion domain enabled determination of volumetric flow, which ranged from 9.03 to 44.9 mL/s ( $25.2 \pm 10.3$  mL/s). These estimates are supported by Doppler ultrasound results. **Conclusions** The dynamic contrast-

enhanced magnetic resonance imaging analysis described here provides quantitative estimates of the number of maternal perfusion domains in a primate placenta and estimates flow within each domain. Anticipated extensions of this technique are to the study placental function in non-human primate models of obstetric complications. © 2014 Wiley Periodicals, Inc.

Gallego-Villar, L., Viecelli, H. M., Pérez, B., Harding, C. O., Ugarte, M., Thöny, B., et al. (2014). A sensitive assay system to test antisense oligonucleotides for splice suppression therapy in the mouse liver. *Molecular Therapy - Nucleic Acids*, 3, e193.

We have previously demonstrated the efficacy of antisense therapy for splicing defects in cellular models of metabolic diseases, suppressing the use of cryptic splice sites or pseudoexon insertions. To date, no animal models with these defects are available. Here, we propose exon skipping of the phenylalanine hydroxylase (Pah) gene expressed in liver and kidney to generate systemic hyperphenylalaninemia in mice as a sensitive in vivo assay to test splice suppression. Systemic elevation of blood L-Phe can be quantified using tandem MS/MS. Exon 11 and/or 12 skipping for the normal PAH gene was validated in hepatoma cells for comparing two oligonucleotide chemistries, morpholinos and locked nucleic acids. Subsequently, Vivo-morpholinos (VMO) were tested in wild-type and in phenotypically normal Pahenu2/+ heterozygous mice to target exon 11 and/or 12 of the murine Pah gene using different VMO dosing, mode of injection and treatment regimes. Consecutive intravenous injections of VMO resulted in transient hyperphenylalaninemia correlating with complete exon skipping and absence of PAH protein and enzyme activity. Sustained effect required repeated injection of VMOs. Our results provide not only a sensitive in vivo assay to test for splice-modulating antisense oligonucleotides, but also a simple method to generate murine models for genetic liver diseases. © 2014 The American Society of Gene & Cell Therapy All rights reserved.

Gamble, B. T., Brush, M., Zirkle, M., Finch, D., Reeves, R., Hickham, D., et al. (2014). Post-traumatic stress disorder (PTSD) ontology and use case. *5th International Conference on Biomedical Ontology, ICBO 2014*, , 1327. pp. 56-59.

Ontologies play an increasingly important role in annotation, integration, and analysis of biomedical data. In this paper, we describe the design and development of a Post-Traumatic

Stress Disorder (PTSD) Ontology and how we can use this ontology as a controlled vocabulary for supporting automatic annotation of clinical text. The automated annotation is performed using a natural language processing (NLP) tool called YTEX. In addition, we demonstrate how we can use the concepts and relationships defined in the PTSD Ontology to perform data summarization and categorization.

Gandhi, R. R., Overton, T. L., Haut, E. R., Lau, B., Vallier, H. A., Rohs, T., et al. (2013). Optimal timing of femur fracture stabilization in polytrauma patients: A practice management guideline from the eastern association for the surgery of trauma. *Journal of Trauma and Acute Care Surgery*, 77(5), 787-795.

Background: Femur fractures are common among trauma patients and are typically seen in patients with multiple injuries resulting from high-energy mechanisms. Internal fixation with intramedullary nailing is the ideal method of treatment; however, there is no consensus regarding the optimal timing for internal fixation. We critically evaluated the literature regarding the benefit of early (G24 hours) versus late (924 hours) open reduction and internal fixation of open or closed femur fractures on mortality, infection, and venous thromboembolism (VTE) in trauma patients. Methods: A subcommittee of the Practice Management Guideline Committee of the Eastern Association for the Surgery of Trauma conducted a systematic review and meta-analysis for the earlier question. RevMan software was used to generate forest plots. Grading of Recommendations, Assessment, Development, and Evaluations methodology was used to rate the quality of the evidence, using GRADEpro software to create evidence tables. RESULTS: No significant reduction in mortality was associated with early stabilization, with a risk ratio (RR) of 0.74 (95% confidence interval [CI], 0.50-1.08). The quality of evidence was rated as "low." No significant reduction in infection (RR, 0.4; 95% CI, 0.10-1.6) or VTE (RR, 0.63; 95% CI, 0.37-1.07) was associated with early stabilization. The quality of evidence was rated "low."

Conclusion: In trauma patients with open or closed femur fractures, we suggest early (G24 hours) open reduction and internal fracture fixation. This recommendation is conditional because the strength of the evidence is low. Early stabilization of femur fractures shows a trend (statistically insignificant) toward lower risk of infection, mortality, and VTE. Therefore, the panel

concludes the desirable effects of early femur fracture stabilization probably outweigh the undesirable effects in most patients. Copyright © 2014 by Lippincott Williams & Wilkins).

García-Tornadu, I., Risso, G., Perez-Millan, M. I., Noain, D., Diaz-Torga, G., Low, M. J., et al. (2010).

*Neurotransmitter modulation of the GHRH-GH axis* S. Karger AG.

The role of dopaminergic receptors in the control of GH release remains controversial. The dopamine receptor 2 (D2R) knockout mouse represents a useful model to study the participation of the D2R on growth and GHRH-GH regulation. These knockout mice have hyperprolactinemia and lactotrope hyperplasia, but unexpectedly, they are also growth retarded. In D2R knockout mice there is a significant decrease in somatotrope population, which is paralleled by decreased GH content and output from pituitary cells. The sensitivity of GHRH-induced GH and cAMP release is similar between genotypes, even though the response amplitude is lower in knockouts. We point to an involvement of D2R signaling at the hypothalamic level as dopamine did not release GH acting at the pituitary level, and both somatostatin and GHRH mRNA expression are altered in knockout mice. The similarity of the pituitary defect in the D2R knockout mouse to that of GHRH deficient models suggests a probable mechanism. Loss of dopamine signaling via hypothalamic D2Rs at a critical age may cause inadequate GHRH secretion subsequently leading to inappropriate somatotrope lineage development. Furthermore, GH pulsatility, which depends on a regulated temporal balance between GHRH and somatostatin output might be compromised in D2R knockout mice, leading to lower IGF-I, and growth retardation. © 2010 S. Karger AG, Basel.

Garzotto, M. (2008). *The natural and treated history of prostate cancer* Cambridge University Press.

Introduction Adenocarcinoma of the prostate is the most common visceral cancer of industrialized nations and the second most lethal cancer among men. In the United States alone, 186 000 new cases are expected and over 28 000 men will die from this disease in 2008 [1]. Therefore, while prostate cancer is a leading cause of cancer death, the vast majority of men survive the disease and ultimately die of other causes. Currently it is estimated that a man's lifetime risk of being diagnosed with prostate cancer is 1 in 6. These odds are expected to increase as the combination of improved medical therapy and lifestyle modifications lead to prolonged population longevity. It is well known that not all prostate cancer patients will benefit from interventions with curative

intent as many tumors will remain indolent throughout the patient's life. In fact it is estimated that only 3% of all men, or about 1 in 6 of all prostate cancer patients, will die of this disease. Nevertheless, a significant proportion of prostate cancer patients who die of other causes may well suffer from disease progression or treatment complications during their lifetime. Thus, the clinical sequelae of prostate cancer can be quite variable, ranging from the tumor being discovered incidentally without any symptoms, to patients presenting with widely metastatic, treatment-resistant disease that is rapidly fatal. Thus prostate cancer often presents perplexing management questions to clinicians who treat this disease. © Cambridge University Press 2009.

Geltzeiler, C. B., Wieghard, N., & Tsikitis, V. L. (2014). Recent developments in the surgical management of perianal fistula for Crohn's disease. *Annals of Gastroenterology*, 27(4), 320-330. Perianal manifestations of Crohn's disease (CD) are common and, of them, fistulas are the most common. Perianal fistulas can be extremely debilitating for patients and are often very challenging for clinicians to treat. CD perianal fistulas usually require multidisciplinary and multimodality treatment, including both medical and surgical approaches. The majority of patients require multiple surgical interventions. CD patients with perianal fistulas have a high rate of primary nonhealing, surgical morbidity, and high recurrence rates. This has led to constant efforts to improve surgical management of this disease process. © 2014 Hellenic Society of Gastroenterology.

Geltzeiler, M., Li, G., Abraham, J., & Keller, C. (2015). The case for primary salivary rhabdomyosarcoma. *Frontiers in Oncology*, 5, 74.

Rhabdomyosarcomas of the parotid and submandibular glands have the histological appearance of a skeletal muscle tumor yet can be found in tissue with no striated muscular elements. We examine the potential cell-of-origin for rhabdomyosarcoma and whether salivary tumors represent primary malignancy or metastasis. We have previously established genetically engineered mouse models of rhabdomyosarcoma. In these mice, rhabdomyosarcoma is only induced when a Pax3:Foxo1 fusion oncogene is activated with concurrent loss of p53 function (for alveolar rhabdomyosarcoma) or loss of p53 function alone (for embryonal rhabdomyosarcoma) using Cre-lox technology. These mutations are only activated under the control of promoters

specific for selected cell lineages, previously thought to be myogenesis-restricted. RT-PCR and immunohistochemistry for lineage-specific promoter gene products reveal these promoters are active in wild-type mouse salivary gland. Given that mouse rhabdomyosarcoma frequently originates in the salivary glands and these myogenic-related promoters are normally expressed in salivary tissue, a high likelihood exists that the salivary gland contains a cell-of-origin of this muscle-related cancer.

Gilhooly, J., Redden, H. R., & Leonard, D. T. (2015). Competency in neonatal endotracheal intubation: Mission impossible? *Pediatrics*, *135*(5), e1290-1.

Gomez, J. L., & Ryabinin, A. E. (2014). The effects of ghrelin antagonists [D-Lys3]-GHRP-6 or JMV2959 on ethanol, water, and food intake in C57BL/6J mice. *Alcoholism: Clinical and Experimental Research*, *38*(9), 2436-2444.

Background: Alcohol use and abuse patterns have created a need for novel treatment models. Current research has turned its focus on reward pathways associated with intrinsic necessities, such as feeding. Theories suggest that drugs of abuse seize control of natural reward pathways and dysregulate normal function, leading to chronic addiction. One such pathway involving the hunger stimulating peptide, ghrelin, is the focus of our study. Methods: Male C57BL/6J mice were randomly assigned to groups and treated with vehicle or a ghrelin antagonist, either [D-Lys3]-GHRP-6 (DLys) or JMV2959. Three experiments tested ghrelin antagonism using different doses; experiment 1 tested 12 mg/kg JMV2959; experiment 2 tested 15 mg/kg DLys; experiment 3 tested 9 mg/kg JMV2959. Using a 2-bottle choice 24-hour access paradigm, data were collected for ethanol intake, preference, water intake, and food intake at 4 and 24 hours after injection. Results: Experiment 1 showed that 12 mg/kg of JMV2959 decreased ethanol, water, and food intake, without affecting preference. Experiment 2 showed that 15 mg/kg of DLys decreased ethanol intake, preference, and water intake only on the first day of treatment. Experiment 3 showed that 9 mg/kg of JMV2959 decreased only ethanol and food intake. No change was seen during deprivation, and JMV2959 was still effective at reducing ethanol intake upon reintroduction. Despite the change in food intake, there were no differences in body weight throughout the experiments. It should be noted that the majority of significant effects were only

found 4 hours postinjection. Conclusions: The results show that compounds that block ghrelin receptor activity are effective at decreasing ethanol intake. However, DLys was only effective at reducing intake and preference on the first day, suggesting a quick tolerance and selectivity for ethanol. JMV2959 consistently reduced ethanol intake, but at the higher dose also reduced all other consummatory behaviors. Thus, ghrelin antagonists provide a viable potential for treatment of alcohol abuse disorders, but further research is needed to determine an appropriate dose and administration paradigm. © 2014 by the Research Society on Alcoholism.

Gordon, M. A., Lasater, K., Brunett, P., & Dieckmann, N. F. (2015). Interprofessional education:

Finding a place to start. *Nurse Educator*,

The Institute of Medicine has recommended interprofessional education (IPE) to improve patient safety and quality outcomes. However, getting started in IPE can be overwhelming and fraught with barriers. One health science university began by offering a 2-week intensive course that was integrated into existing courses. The evaluation validated the need for more understanding about professional roles and preparation as well as for faculty to learn from each other.

Grant, K. A., Stafford, J., Thiede, A., Kiley, C., Odagiri, M., & Ferguson, B. (2008). Who is at risk?

population characterization of alcohol self-administration in nonhuman primates helps identify pathways to dependence. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(4), 289-297.

Alcohol abuse and dependence are human conditions for which no full equivalent exists in animals. Nevertheless, animal models frequently are used to study various aspects of alcohol dependence that cannot be easily or ethically assessed in humans, including neurobiological mechanisms underlying alcohol dependence. Many of these animal models involve rodents; however, the characteristics (i.e., phenotypes) of chronic heavy drinking may be limited in these species. Nonhuman primates add an important translational aspect to the study of alcohol abuse and alcoholism. Their genetic, anatomical, physiological, and behavioral similarity to humans offers unique opportunities for identifying risk factors that may predispose a person to or accelerate the course of alcohol addiction. Studying alcohol consumption in nonhuman primates, including the distribution of drinking levels in a population, also can be uniquely informative to

alcohol research. For example, research on the self-administration procedures in primates can help scientists identify risk factors for excessive alcohol consumption in humans. The phenotype of excessive drinking then can serve as the starting point to test and verify the underlying genetic and environmental influences. The resulting findings, in turn, can help guide prevention and treatment strategies.

Gray, N. E., & Quinn, J. F. (2015). Alterations in mitochondrial number and function in Alzheimer's disease fibroblasts. *Metabolic Brain Disease*,

Mitochondrial dysfunction is observed in brains of Alzheimer's Disease patients as well as many rodent model systems including those modeling mutations in presenilin 1 (PSEN1). The aim of our study was to characterize mitochondrial function and number in fibroblasts from AD patients with PSEN1 mutations. We used biochemical assays, metabolic profiling and fluorescent labeling to assess mitochondrial number and function in fibroblasts from three AD patients compared to fibroblasts from three controls. The mutant AD fibroblasts had increased Abeta42 relative to controls along with reduction in ATP, basal and maximal mitochondrial respiration as well as impaired spare mitochondrial respiratory capacity. Fluorescent staining and expression of genes encoding electron transport chain enzymes showed diminished mitochondrial content in the AD fibroblasts. This study demonstrates that mitochondrial dysfunction is observable in AD fibroblasts and provides evidence that this model system could be useful as a tool to screen disease-modifying compounds.

Gross, O. P., Pugh, E. N., Jr., & Burns, M. E. (2015). cGMP in mouse rods: The spatiotemporal dynamics underlying single photon responses. *Frontiers in Molecular Neuroscience*, 8(MAR)

Vertebrate vision begins when retinal photoreceptors transduce photons into electrical signals that are then relayed to other neurons in the eye, and ultimately to the brain. In rod photoreceptors, transduction of single photons is achieved by a well-understood G-protein cascade that modulates cGMP levels, and in turn, cGMP-sensitive inward current. The spatial extent and depth of the decline in cGMP during the single photon response (SPR) have been major issues in phototransduction research since the discovery that single photons elicit substantial and reproducible changes in membrane current. The spatial profile of cGMP decline

during the SPR affects signal gain, and thus may contribute to reduction of trial-to-trial fluctuations in the SPR. Here we summarize the general principles of rod phototransduction, emphasizing recent advances in resolving the spatiotemporal dynamics of cGMP during the SPR.

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Grove, M., & Emch, J. (2014). An ontologic approach to leverage surgical training data: Development and application of a craniomaxillofacial ontology. *5th International Conference on Biomedical Ontology, ICBO 2014*, , 1327. pp. 104-105.

Oral and maxillofacial surgery (OMS) is a surgical specialty involving procedures on the neck and head. OMS training program accreditation and evaluation requires reporting the surgical experiences of trainees. Current systems for tracking these experiences are based on coarse payment coding systems. To provide more granular training data, we are developing an ontology-driven surgical resident training log (OMSLog). We use a blended architecture consisting of an interface for trainees, faculty, and/or administrators to record surgical experiences, a traditional relational database back-end for data storage, with both supported by a new domain ontology. The CranioMaxilloFacial (CMF) ontology is built on a SNOMED CT foundation and is extended to include granular domain concepts and educational experiences. Current results are a pilot graphical user interface (GUI) driven by a >7,000 concept domain ontology. Future steps include pilot testing in the residency program and ontological alignment with the Human Phenotype Ontology (HPO).

Grow, E. J., Flynn, R. A., Chavez, S. L., Bayless, N. L., Wossidlo, M., Wesche, D. J., et al. (2015).

Intrinsic retroviral reactivation in human preimplantation embryos and pluripotent cells. *Nature*, Endogenous retroviruses (ERVs) are remnants of ancient retroviral infections, and comprise nearly 8% of the human genome. The most recently acquired human ERV is HERVK(HML-2), which repeatedly infected the primate lineage both before and after the divergence of the human and chimpanzee common ancestor. Unlike most other human ERVs, HERVK retained multiple copies of intact open reading frames encoding retroviral proteins. However, HERVK is transcriptionally silenced by the host, with the exception of in certain pathological contexts such as germ-cell tumours, melanoma or human immunodeficiency virus (HIV) infection. Here we

demonstrate that DNA hypomethylation at long terminal repeat elements representing the most recent genomic integrations, together with transactivation by OCT4 (also known as POU5F1), synergistically facilitate HERVK expression. Consequently, HERVK is transcribed during normal human embryogenesis, beginning with embryonic genome activation at the eight-cell stage, continuing through the emergence of epiblast cells in preimplantation blastocysts, and ceasing during human embryonic stem cell derivation from blastocyst outgrowths. Remarkably, we detected HERVK viral-like particles and Gag proteins in human blastocysts, indicating that early human development proceeds in the presence of retroviral products. We further show that overexpression of one such product, the HERVK accessory protein Rec, in a pluripotent cell line is sufficient to increase IFITM1 levels on the cell surface and inhibit viral infection, suggesting at least one mechanism through which HERVK can induce viral restriction pathways in early embryonic cells. Moreover, Rec directly binds a subset of cellular RNAs and modulates their ribosome occupancy, indicating that complex interactions between retroviral proteins and host factors can fine-tune pathways of early human development.

Guan, H. B., Nie, Y. Z., Zheng, Y. W., Takiguchi, K., Yu, H. W., Zhang, R. R., et al. (2015). Acyclic retinoid induces differentiation and apoptosis of murine hepatic stem cells. *Stem Cell Research & Therapy*, 6(1), 51.

**INTRODUCTION:** The therapeutic potential of acyclic retinoid (ACR), a synthetic retinoid, has been confirmed in experimental and clinical studies. Therapeutic targets include precancerous and cancer stem cells. As ACR is also involved in developmental processes, its effect on normal hepatic stem cells (HpSCs) should be investigated for understanding the underlying mechanisms. Here, we examined effects of the acyclic retinoid peretinoin on fresh isolated murine HpSCs.

**METHODS:** We isolated c-kit-CD29+CD49f+/lowCD45-Ter119- cells from murine fetal livers using flow cytometry. To evaluate the effect of ACR, we traced clonal expansion and analyzed cell differentiation as well as apoptosis during the induction process by immunofluorescent staining and marker gene expression.

**RESULTS:** ACR dose-dependently inhibited HpSCs expansion. Stem cell clonal expansion was markedly inhibited during the culture period. Moreover, ACR showed a significant promotion of HpSC differentiation and induction of cellular apoptosis. The expression of stem cell marker genes, *Afp*, *Cd44*, and *Dlk*, was downregulated, while that of mature

hepatocyte genes, Alb and Tat, and apoptosis-related genes, Annexin V and Caspase-3, were upregulated. Flow cytometry showed that the proportion of Annexin V-positive cells increased after ACR incubation compared with the control. Data obtained by immunofluorescent staining for albumin and Caspase-3 corroborated the data on gene expression. Finally, we found that ACR directly regulates the expression of retinoic acid receptors and retinoid X receptors.

CONCLUSIONS: These findings indicate that ACR inhibits the clonal expansion of normal HpSCs in vitro and promotes the differentiation of immature cells by regulating receptors of retinoic acid.

Gubner, N. R., & Phillips, T. J. (2015). Effects of nicotine on ethanol-induced locomotor sensitization: A model of neuroadaptation. *Behavioural Brain Research, 288*, 26-32.

Co-morbid use of nicotine-containing tobacco products and alcohol (ethanol) is prevalent in young adults initiating use and in alcohol dependent adults, suggesting that these drugs in combination may increase risk to develop dependence on one or both drugs. Neuroadaptations caused by repeated drug exposure are related to the development of drug dependence and vulnerability to relapse. Locomotor sensitization has been used as a behavioral measure used to detect changes in neural drug sensitivity that are thought to contribute to drug dependence and relapse. Locomotor sensitization was measured in the current studies to examine potential differences in the effects of nicotine and ethanol given alone and in combination. Baseline activity levels of DBA/2J mice were assessed on 2 days, then mice were treated for 10 days with saline, nicotine (1 or 2mg/kg of nicotine tartrate), ethanol (1 or 2g/kg), or nicotine plus ethanol and locomotor activity was assessed every third day. On the following day, all mice were challenged with ethanol to measure the expression of sensitization. Mice treated with both nicotine and ethanol exhibited greater stimulation than predicted from the combined independent effects of these drugs, consistent with our previously published results. The combined effects of nicotine and ethanol on locomotor sensitization were dependent on the dose of ethanol and whether testing was performed after the drugs were given together, or after challenge with ethanol alone. These results suggest that nicotine and ethanol in combination can have neuroadaptive effects that differ from the independent effects of these drugs.

Guseh, S. H., Feinberg, B. B., Dawood, H. Y., Yamamoto, H. S., Fichorova, R. N., & Burwick, R. M.

(2015). Urinary excretion of C5b-9 is associated with the anti-angiogenic state in severe preeclampsia. *American Journal of Reproductive Immunology*, 73(5), 437-444.

Problem: Severe preeclampsia has been independently linked to complement dysregulation and angiogenic imbalance; however, the relationship between complement and angiogenic factors in human pregnancy is unclear. Method of study: Utilizing existing biomarkers, our study sought to better understand this relationship in active disease. We performed a case-control study, enrolling 25 cases with severe preeclampsia, 25 controls with chronic hypertension, and 25 healthy controls without hypertension. Levels of complement components (C3a, C5a, and C5b-9) and angiogenic markers [basic fibroblast growth factor (bFGF), placental growth factor (PlGF), vascular endothelial growth factor (VEGF), and soluble fms-like tyrosine kinase-1 (sFlt-1)] were measured simultaneously. Results: Compared to both hypertensive and non-hypertensive controls, severe preeclampsia was associated with increased plasma sFlt-1, decreased plasma VEGF and PlGF, decreased urinary PlGF, and increased urinary C5b-9. Urinary marker C5b-9 correlated strongly with the anti-angiogenic condition. In subjects with detectable urinary excretion of C5b-9, median plasma levels of sFlt-1 were significantly greater (32,029 versus 4556 pg/mL,  $P < 0.0001$ ) and levels of PlGF (15.6 versus 226 pg/mL,  $P < 0.0001$ ) and VEGF (119 versus 153 pg/mL,  $P = 0.001$ ) were significantly lower. Conclusion: More so than plasma complement markers, urinary C5b-9 may be a useful measure to link complement dysregulation with angiogenic imbalance in severe preeclampsia. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Gustin, J. K., Bai, Y., Moses, A. V., & Douglas, J. L. (2015). Ebola virus glycoprotein promotes

enhanced viral egress by preventing ebola VP40 from associating with the host restriction factor BST2/Tetherin. *The Journal of Infectious Diseases*,

BACKGROUND: BST2/tetherin is an innate immune molecule with the unique ability to restrict the egress of human immunodeficiency virus (HIV) and other enveloped viruses, including Ebola virus (EBOV). Coincident with this discovery was the finding that the HIV Vpu protein down-regulates BST2 from the cell surface, thereby promoting viral release. Evidence suggests that the EBOV envelope glycoprotein (GP) also counteracts BST2, although the mechanism is unclear. RESULTS:

We find that total levels of BST2 remain unchanged in the presence of GP, whereas surface BST2 is significantly reduced. GP is known to sterically mask surface receptors via its mucin domain. Our evaluation of mutant GP molecules indicate that masking of BST2 by GP is probably responsible for the apparent surface BST2 down-regulation; however, this masking does not explain the observed virus-like particle egress enhancement. We discovered that VP40 coimmunoprecipitates and colocalizes with BST2 in the absence but not in the presence of GP. CONCLUSIONS: These results suggest that GP may overcome the BST2 restriction by blocking an interaction between VP40 and BST2. Furthermore, we have observed that GP may enhance BST2 incorporation into virus-like particles. Understanding this novel EBOV immune evasion strategy will provide valuable insights into the pathogenicity of this deadly pathogen.

Hahn, P. F., Guimaraes, A. R., Arellano, R. S., Mueller, P. R., & Gervais, D. A. (2015). Nonvascular interventional procedures in an urban general hospital. analysis of 2001-2010 with comparison to the previous decade. *Academic Radiology*,

Rationale and Objectives: To determine trends in nonvascular image-guided procedures at an urban general hospital over a 10-year period and to compare utilization of nonvascular interventional radiology (IR) over the decade 2001-2010 to a previously reported analysis for 1991-2000. Methods: With institutional review board approval, a 20-year quality assurance database verified against the radiology information system was queried for procedure location (eg, pleura, liver, bowel, and abdomen) and type (eg, biopsy, catheter insertion, and transient drainage), demographics, and change over time. Yearly admissions and new hospital numbers assigned each year served to normalize for overall hospital activity. Results: A total of 50,195 IR procedures were performed in 24,309 distinct patients (male:female, 12,625:11,684; average age, 60 years), 940 procedures performed in age <20 years, and 571 procedures performed in patients aged  $\geq 90$  years. A total of 15345, 4377, and 1754 patients had one, two, or three procedures, respectively; 470 had  $\geq 10$  procedures. Twenty-seven supervising radiologists and 277 individuals participated as operators, double the previous decade. Biopsy (4.8% average yearly increase), abdominal drainage (7.3%), paracentesis (12.9%), tube manipulation (13.0%), suprapubic bladder tube insertion (21.0%), and gastrostomy (44.6%) all increased strongly ( $P < .001$ ) over 120 months but not biliary drainage, nephrostomy, or chest tubes. Procedures

increased faster than either admissions or new hospital numbers ( $P < .001$ ). For each 1000 new hospital numbers, IR service performed 48 procedures versus 31 the previous decade ( $P < .0005$ ).  
Conclusions: Referrals for nonvascular IR procedures have doubled over 2 decades, outpacing growth in new hospital patients and requiring increased resource allocation. © 2015 AUR.

Hajar, T., Fernandez-Martinez, R., Moreno-Coutino, G., Vasquez Del Mercado, E., & Arenas, R. (2015).

Modified PAS stain: A new diagnostic method for onychomycosis. *Revista Iberoamericana De Micologia*,

**BACKGROUND:** Onychomycosis is the most common nail disease and represents around 50% of nail disorders. Accurate diagnosis with adequate evidence is ideal before starting any treatment. Current diagnostic methods offer low specificity and sensitivity. **AIMS:** To create a new method for the diagnosis of onychomycosis, and to compare its sensitivity and specificity with the existing methods. **METHODS:** One hundred and ninety-two samples with clinical suspicion of onychomycosis were included and underwent modified PAS stain (M-PAS), KOH/chlorazol black (KOH/CB) and culture testing. Sensitivity, specificity, positive and negative predictive values were calculated. **RESULTS:** In 152 out of 192 samples (79.2%) fungi structures were found in at least one of the three tests performed, and the patients were diagnosed with onychomycosis; 40 samples out of 192 (20.8%) were negative. Using M-PAS, filaments and/or spores were seen in 143 samples from the 152 positive (94%); 39 of them were negative to KOH/CB and positive to M-PAS (25.6%). With KOH/CB, filaments and/or spores were seen in 113 cases from the 152 positive samples (73.8% of the onychomycosis cases). Thirty-five cultures were positive, of which 77% were identified as *Trichophyton rubrum*; 117 onychomycosis cases were diagnosed despite the negative culture (76.9%). M-PAS showed 92.5% sensitivity and 55.55% specificity, a 67.5% positive predictive value and a 81.6% negative productive value. **CONCLUSIONS:** This procedure, a combination of the existing methods to diagnose onychomycosis, KOH/CB together with a nail clipping biopsy, proved to have high sensitivity, as well as being rapid, easy, inexpensive and readily available in most hospital settings. M-PAS allowed us to diagnose 39 cases (25.6% of the cases of onychomycosis) that were false negative using only KOH/CB and culture.

Hamilton, K. R., Mitchell, M. R., Wing, V. C., Balodis, I. M., Bickel, W. K., Fillmore, M., et al. (2015).

Choice impulsivity: Definitions, measurement issues, and clinical implications. *Personality Disorders*, 6(2), 182-198.

Impulsivity critically relates to many psychiatric disorders. Given the multifaceted construct that impulsivity represents, defining core aspects of impulsivity is vital for the assessment and understanding of clinical conditions. Choice impulsivity (CI), involving the preferential selection of smaller sooner rewards over larger later rewards, represents one important type of impulsivity. The International Society for Research on Impulsivity (InSRI) convened to discuss the definition and assessment of CI and provide recommendations regarding measurement across species. Commonly used preclinical and clinical CI behavioral tasks are described, and considerations for each task are provided to guide CI task selection. Differences in assessment of CI (self-report, behavioral) and calculating CI indices (e.g., area-under-the-curve, indifference point, and steepness of discounting curve) are discussed along with properties of specific behavioral tasks used in preclinical and clinical settings. The InSRI group recommends inclusion of measures of CI in human studies examining impulsivity. Animal studies examining impulsivity should also include assessments of CI and these measures should be harmonized in accordance with human studies of the disorders being modeled in the preclinical investigations. The choice of specific CI measures to be included should be based on the goals of the study and existing preclinical and clinical literature using established CI measures. (PsycINFO Database Record

Hand, R. K., Jordan, B., DeHoog, S., Pavlinac, J., Abram, J. K., & Parrott, J. S. (2015). Inpatient staffing needs for registered dietitian nutritionists in 21st century acute care facilities. *Journal of the Academy of Nutrition and Dietetics*,

Harper, L. M., Caughey, A. B., Roehl, K. A., Odibo, A. O., & Cahill, A. G. (2015). Defining an abnormal first stage of labor based on maternal and neonatal outcomes. *Obstetrical and Gynecological Survey*, 69(10), 575-577.

Heintzman, J., Marino, M., Hoopes, M., Bailey, S. R., Gold, R., O'Malley, J., et al. (2015). Supporting health insurance expansion: Do electronic health records have valid insurance verification and enrollment data? *Journal of the American Medical Informatics Association : JAMIA*,

OBJECTIVE: To validate electronic health record (EHR) insurance information for low-income pediatric patients at Oregon community health centers (CHCs), compared to reimbursement data and Medicaid coverage data. MATERIALS AND METHODS: Subjects Children visiting any of 96 CHCs (N = 69 189) from 2011 to 2012. Analysis The authors measured correspondence (whether or not the visit was covered by Medicaid) between EHR coverage data and (i) reimbursement data and (ii) coverage data from Medicaid. RESULTS: Compared to reimbursement data and Medicaid coverage data, EHR coverage data had high agreement (87% and 95%, respectively), sensitivity (0.97 and 0.96), positive predictive value (0.88 and 0.98), but lower kappa statistics (0.32 and 0.49), specificity (0.27 and 0.60), and negative predictive value (0.66 and 0.45). These varied among clinics. DISCUSSION/CONCLUSIONS: EHR coverage data for children had a high overall correspondence with Medicaid data and reimbursement data, suggesting that in some systems EHR data could be utilized to promote insurance stability in their patients. Future work should attempt to replicate these analyses in other settings.

Helms, C. M., Bell, R. L., Bennett, A. J., Davies, D. L., Chester, J. A., Kosten, T. A., et al. (2015). The importance of animals in advancing research on alcohol use disorders. *Alcoholism, Clinical and Experimental Research*, 39(4), 575-578.

Heppner, K. M., & Perez-Tilve, D. (2015). GLP-1 based therapeutics: Simultaneously combating T2DM and obesity. *Frontiers in Neuroscience*, 9, 92.

Glucagon-like peptide-1 (GLP-1) enhances meal-related insulin secretion, which lowers blood glucose excursions. In addition to its incretin action, GLP-1 acts on the GLP-1 receptor (GLP-1R) in the brain to suppress feeding. These combined actions of GLP-1R signaling cause improvements in glycemic control as well as weight loss in type II diabetes (T2DM) patients treated with GLP-1R agonists. This is a superior advantage of GLP-1R pharmaceuticals as many other drugs used to treat T2DM are weight neutral or actual cause weight gain. This review summarizes GLP-1R action on energy and glucose metabolism, the effectiveness of current GLP-1R agonists on weight loss in T2DM patients, as well as GLP-1R combination therapies.

Hernandez-Rapp, J., Smith, P. Y., Filali, M., Goupil, C., Planel, E., Magill, S. T., et al. (2015). Memory formation and retention are affected in adult miR-132/212 knockout mice. *Behavioural Brain*

*Research, 287, 15-26.*

The miR-132/212 family is thought to play an important role in neural function and plasticity, while its misregulation has been observed in various neurodegenerative disorders. In this study, we analyzed 6-month-old miR-132/212 knockout mice in a battery of cognitive and non-cognitive behavioral tests. No significant changes were observed in reflexes and basic sensorimotor functions as determined by the SHIRPA primary screen. Accordingly, miR-132/212 knockout mice did not differ from wild-type controls in general locomotor activity in an open-field test. Furthermore, no significant changes of anxiety were measured in an elevated plus maze task. However, the mutant mice showed retention phase defects in a novel object recognition test and in the T-water maze. Moreover, the learning and probe phases in the Barnes maze were clearly altered in knockout mice when compared to controls. Finally, changes in BDNF, CREB, and MeCP2 were identified in the miR-132/212-deficient mice, providing a potential mechanism for promoting memory loss. Taken together, these results further strengthen the role of miR-132/212 in memory formation and retention, and shed light on the potential consequences of its deregulation in neurodegenerative diseases.

Heston, A. H., Schwartz, A. L., Justice-Gardiner, H., & Hohman, K. H. (2015). Addressing physical activity needs of survivors by developing a community-based exercise program: LIVESTRONG(R) at the YMCA. *Clinical Journal of Oncology Nursing, 19*(2), 213-217.

BACKGROUND: Although methods of cancer detection and treatment have improved, the side effects of treatment can cause profound debilitation that may linger years after treatment ends. Exercise during and after cancer treatment is safe, and it minimizes many of the deleterious physical and emotional side effects. With this evidence in mind, the LIVESTRONG Foundation and the YMCA of the USA collaborated to develop a community-based physical activity program for survivors, LIVESTRONG(R) at the YMCA. OBJECTIVES: This article provides in-depth information about the development of the LIVESTRONG at the YMCA program and its subsequent spread to meet the physical activity needs of survivors across the country. METHODS: Participating YMCAs engage in regular data collection efforts to track progress on organizational change and program delivery. These efforts include a staff evaluation survey, functional assessment of participants, patient-reported health status assessment, and patient program evaluation. FINDINGS: From the

time of its development, the LIVESTRONG at the YMCA program has served more than 29,000 survivors and trained more than 2,200 LIVESTRONG at the YMCA instructors. A national survey of more than 1,600 program participants demonstrates positive outcomes on health and well-being, as well as intent to continue exercising after the program's end.

Hitzemann, R., Belknap, J. K., & McWeeney, S. K. (2008). Quantitative trait locus analysis: Multiple cross and heterogeneous stock mapping. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(3), 261-265.

Until well into the 1990s, both preclinical and clinical research focused on finding "the" gene for human diseases, including alcoholism. This focus was reinforced by the emergence of technologies to either inactivate (i.e., knock out) a gene or add extra copies of an existing gene in a living organism, which clearly demonstrated that over- or underexpressing a single gene could have a profound effect on behavior. However, a small but vocal group of scientists, including many alcohol researchers, argued that behaviors, including alcohol-related behaviors, were complex traits and therefore no one gene likely would have a large effect. This view was consistent with a large body of genetic research conducted in plants and fruit flies (e.g., Paterson et al. 1988) indicating that, for example, even a presumably simple characteristic, such as the size of a tomato, was determined by several genes. However, it was difficult to convince the scientific community that, in terms of its genetic determination, behavior was similar to the size of a tomato. Only with the advent of new genetic tools did it become possible to prove that many different genes contribute to complex behavioral characteristics.

Hitzemann, R., & Oberbeck, D. (2008). Strategies to study the neuroscience of alcoholism:

Introduction. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(3), 231-232.

Alcohol use and abuse are widespread in the U.S. population. Moreover, for each drinker, alcohol consumption, particularly at excessive levels, has a vast range of effects on the body.

Accordingly, research programs aimed at understanding alcohol's effects on the individual as well as on society are similarly varied and widespread. Much of this research focuses on alcohol's impact on the brain and individual nerve cells (i.e., neurons). A detailed survey of the strategies

used to investigate the neural mechanisms associated with alcohol use and abuse would easily fill multiple volumes. Instead, this Special Section provides brief reviews of topics largely associated with two areas of research: 1) What strategies can researchers use to image the acute and chronic effects of alcohol on brain function? 2) How can investigators detect the genes, gene products, and gene networks associated with alcohol-related traits?

Hodnett, B. L., Schmitt, N. C., Clayburgh, D. R., Burkowsky, A., Balzer, J., Thirumala, P. D., et al. (2015). Superior laryngeal nerve monitoring using laryngeal surface electrodes and intraoperative neurophysiological monitoring during thyroidectomy. *Clinical Anatomy*, 28(4), 460-466.

The objective of this study is to establish normative waveform data for the external branch of the superior laryngeal nerve (SLN) utilizing laryngeal surface electrodes and intraoperative neurophysiological monitoring (IONM) in conjunction with a clinical neurophysiologist. A retrospective chart review of 91 consecutive at-risk SLN were identified in 51 patients in whom IONM using laryngeal surface electrodes was performed by a clinical neurophysiologist using Dragonfly (Neurovision Medical Products, Ventura, CA) recording electrodes and a Protektor (Natus Medical Inc., San Carlos, CA) 16 channel- intraoperative nerve monitoring system. Inclusion criteria were met for 30 SLN. Data collected included preoperative diagnosis, surgical procedure, rates of nerve identification and stimulation, and waveform characteristics. Waveform analysis for 30 SLN yielded a peak latency of  $4.0 \pm 0.2$  ms, onset latency  $2.3 \pm 0.1$  ms, peak-to-peak amplitude of  $220.4 \pm 31.1$   $\mu$ V, onset-to-peak amplitude of  $186.0 \pm 25.0$   $\mu$ V, and stimulation current threshold of  $0.55 \pm 0.03$  mA (data = mean  $\pm$  SEM). Two patients had abnormal SLN function documented clinically on postoperative laryngoscopic examination. Laryngeal surface electrodes were successfully utilized to identify and monitor SLN function intraoperatively. IONM using laryngeal surface electrodes enables analysis of waveform morphology and latency in addition to threshold and amplitude data obtained with the traditional NIM system, potentially improving the performance of nerve monitoring during thyroid surgery. *Clin. Anat.* 28:460-466, 2015. © 2014 Wiley Periodicals, Inc.

Hoehndorf, R., Haendel, M., Stevens, R., & Rebholz-Schuhmann, D. (2014). Thematic series on biomedical ontologies in JBMS: Challenges and new directions. *Journal of Biomedical Semantics*, 5(1)

Over the past 15 years, the biomedical research community has increased its efforts to produce ontologies encoding biomedical knowledge, and to provide the corresponding infrastructure to maintain them. As ontologies are becoming a central part of biological and biomedical research, a communication channel to publish frequent updates and latest developments on them would be an advantage. Here, we introduce the JBMS thematic series on Biomedical Ontologies. The aim of the series is to disseminate the latest developments in research on biomedical ontologies and provide a venue for publishing newly developed ontologies, updates to existing ontologies as well as methodological advances, and selected contributions from conferences and workshops. We aim to give this thematic series a central role in the exploration of ongoing research in biomedical ontologies and intend to work closely together with the research community towards this aim. Researchers and working groups are encouraged to provide feedback on novel developments and special topics to be integrated into the existing publication cycles. © 2014 Hoehndorf et al.; licensee BioMed Central Ltd.

Holliday, E. B., Ahmed, A. A., Jaggi, R., Stentz, N. C., Woodward, W. A., Fuller, C. D., et al. (2015).

Pregnancy and parenthood in radiation oncology, views and experiences survey (PROVES): Results of a blinded prospective trainee parenting and career development assessment.

*International Journal of Radiation Oncology, Biology, Physics*,

PURPOSE: Medical training spans nearly a decade, during which many physicians traditionally begin families. Although childrearing responsibilities are shared by men and women in the modern era, differences in time allocated to child care by sex and its potential impact on residency experience merit discussion. METHODS AND MATERIALS: An anonymous, voluntary, 102-item survey was distributed to 540 current radiation oncology residents and 2014 graduates that asked about marital and parental status, pregnancy during residency, publication productivity, career aspirations, and experiences working with pregnant co-residents. Respondents with children were asked about childcare arrangements, and women who were pregnant during residency were asked about radiation safety, maternity leave, and breastfeeding

experiences. RESULTS: A total of 190 respondents completed the survey, 107 men (56.3%) and 84 women (43.7%). Ninety-seven respondents (51.1%) were parents, and 84 (44.2%) reported a pregnancy during residency. Respondents with children more often were male (65% vs 47.3%;  $P=.014$ ), in a higher level of training (79.3% vs 54.8% were PGY4 or higher;  $P=.001$ ), were older (median age of 32, interquartile range [IQR]:31-35] vs age 30 [IQR: 29-33];  $P<.001$ ), had a PhD (33% vs 19.3%, respectively;  $P=.033$ ), were married (99% vs 43%, respectively;  $P<.001$ ), and had a partner who did not work (24.7% vs 1.9%, respectively;  $<.001$ ). There were no differences in the number of manuscripts published or the number of residents who expressed likelihood of pursuing an academic career by parental status. Among parents, men more frequently had partners who did not work (38.1% vs 0%, respectively;  $P<.001$ ) and reported that their partner performed a greater percentage of childcare duties (70% [IQR: 60%-80%] vs 35% [IQR: 20%-50%], respectively;  $P<.001$ ). CONCLUSIONS: Pregnancy and parenthood are common during residency. Female residents are frequently responsible for more childcare duties than males but have similar research productivity and career aspirations. Further investigation is critical to elucidate gender disparities in parenthood and career development.

Holtan, S. G., Chen, Y., Kaimal, R., Creedon, D. J., Enninga, E. A., Nevala, W. K., et al. (2015).

Growth modeling of the maternal cytokine milieu throughout normal pregnancy: Macrophage-derived chemokine decreases as Inflammation/Counterregulation increases. *Journal of Immunology Research*, 2015, 952571.

Several recent studies have shown differences in the maternal immune milieu at different phases of pregnancy, but most studies have been cross-sectional or of relatively few time points. Levels of 42 cytokines were determined using a multiplex bead-based assay on archived serum from a cohort of pregnant women ( $N = 16$ ) at median of 18 time points tested, from the first trimester through to parturition, per woman. Unconditional growth modeling was then used to determine time-dependent changes in levels of these cytokines. Macrophage-derived chemokine (MDC, aka CCL22) decreases as pregnancy progresses. IL-1beta, IL-6, IL-8, IL-12p70, IL-13, IL-15, IP-10, and FLT3-ligand increase as a function of gestational weeks, and IFNalpha2, IL-1ra, IL-3, IL-9, IL-12p40, and soluble CD40 ligand increase as a function of trimester. As pregnancy normally

progresses, a maternal shift away from a type 2-biased immune response and toward an inflammatory/counterregulatory response is observed.

Hooper, J. E., Hebert, J. F., Schilling, A., Gross, N. D., Schindler, J. S., Lagowski, J. P., et al. (2015).

Hybrid capture 2 is as effective as PCR testing for high-risk human papillomavirus in head and neck cancers. *Applied Immunohistochemistry & Molecular Morphology : AIMM / Official Publication of the Society for Applied Immunohistochemistry*, 23(4), 266-272.

High-risk human papillomavirus (HPV) infection is a common cause of oropharyngeal squamous cell carcinoma, especially in young male nonsmokers. Accurately diagnosing HPV-associated oral cancers is important, because they have a better prognosis and may be treated differently than smoking-related oral carcinomas. Various methods have been validated to test for high-risk HPV in cervical tissue samples, and they are in routine clinical use to detect dysplasia before it progresses to invasive disease. Similarly, future screening for HPV-mediated oropharyngeal dysplasia may identify patients before it progresses. Our objective was to compare 4 of these methods in a retrospective series of 87 oral and oropharyngeal squamous cell carcinomas that had archived fresh-frozen and paraffin-embedded tissue for evaluation. Patient age, sex, smoking history, and tumor location were also recorded. DNA prepared from fresh-frozen tissue was tested for HPV genotypes by multiplex polymerase chain reaction analysis, and high-risk HPV screening was carried out using Hybrid Capture 2 and Cervista. Histologic sections were immunostained for p16. HPV-positive outcome was defined as agreement between at least 2 of the 3 genetic tests and used for chi analysis and calculations of diagnostic predictive value. As expected, high-risk HPV-positive oral cancers were most common in the tonsil and base of the tongue (oropharynx) of younger male (55 vs. 65 y) ( $P=0.0002$ ) nonsmokers ( $P=0.01$ ). Most positive cases were HPV16 (33/36, 92%). Hybrid Capture 2 and Cervista were as sensitive as polymerase chain reaction and had fewer false positives than p16 immunohistochemical staining.

Horner-Johnson, W., Dobbertin, K., & Iezzoni, L. I. (2015). Disparities in receipt of breast and cervical cancer screening for rural women age 18 to 64 with disabilities. *Women's Health Issues : Official Publication of the Jacobs Institute of Women's Health*,

BACKGROUND: Previous research has found breast and cervical cancer screening disparities

between women with and without disabilities, and between women living in rural versus urban areas. Living in a rural area may add to the barriers women with disabilities experience when attempting to obtain screening for breast and cervical cancer. The purpose of this study was to examine the combination of disability status and rurality in association with receipt of breast and cervical cancer screening among women age 18 to 64 in the United States. METHODS: We conducted cross-sectional analyses of data from the Medical Expenditure Panel Survey, using pooled annual data files from 2002 through 2008. We compared recent receipt of breast and cervical cancer screening among four groups: 1) urban women without disabilities, 2) urban women with disabilities, 3) rural women without disabilities, and 4) rural women with disabilities. FINDINGS: Overall, women with disabilities were less likely to be up to date with mammograms and Pap tests compared with women with no disabilities. Similarly, women in rural areas were less likely to have received breast or cervical cancer screening within recommended timeframes. Women who both had a disability and lived in a rural area were the least likely to be current with screening. CONCLUSIONS: Our findings suggest that living in rural regions compounds disparities in receipt of cancer screening among women with disabilities. Increased attention is needed to improve receipt of cancer screening among rural women with disabilities.

Horner-Johnson, W., Dobbertin, K., Lee, J. C., & Andresen, E. M. (2015). Rural disparities in receipt of colorectal cancer screening among adults ages 50-64 with disabilities. *Disability and Health Journal*, 7(4), 394-401.

Background: Colorectal cancer is the third leading cause of cancer deaths in the United States. Early detection can reduce mortality; however, only 59% of U.S. adults age 50 and over meet recommended colorectal cancer screening guidelines. Studies in the general population have observed that rural residents are less likely to have received colorectal cancer screening than residents of urban areas. Objective: To determine whether urban/rural disparities in colorectal cancer screening exist among people with disabilities, similar to the disparities found in the general population. Methods: We analyzed Medical Expenditure Panel Survey annual data files from 2002 to 2008. We conducted logistic regression analyses to examine the relationship between urban/rural residence and ever having received screening for colorectal cancer (via colonoscopy, sigmoidoscopy, or fecal occult blood test). Results: Among U.S. adults ages 50-64

with disabilities, those living in rural areas were significantly less likely to have ever received any type of screening for colorectal cancer. The urban/rural difference was statistically significant regardless of whether or not we controlled for demographic, socioeconomic, health, and health care access variables. Conclusions: Disparity in screening for colorectal cancer places rural residents with disabilities at greater risk for late stage diagnosis and mortality relative to people with disabilities in urban areas. Thus, there is a need for strategies to improve screening among people with disabilities in rural areas. © 2014 Elsevier Inc. All rights reserved.

Hsiao, C. -, Wu, Y. -, Nan, F. -, Huang, S. -, Chen, L., & Chen, S. -. (2015). Immunomodulator 'mushroom beta glucan' induces wnt/ $\beta$  catenin signalling and improves wound recovery in tilapia and rat skin: A histopathological study. *International Wound Journal*,  
The present study aims to investigate the effects of mushroom beta glucan (MBG) on wound recovery in partial hepatectomy (PH) in Nile tilapia (*Oreochromis niloticus*) and in rat skin wound healing examination. Following PH, we focussed on the effects on liver repair ability using in vitro and in vivo tests. In vitro, we examined whether the MBG has an impact on liver cell proliferation, mainly through 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide (MTT) assays and bromodeoxyuridine (BrdU) cell proliferation assay detection method. Results showed that MBG treatment was remarkable in enhancing cell proliferation of hepatocytes and in maintaining the cellular viability. Immunohistochemical staining to analyse Wnt/ $\beta$ -catenin signalling also showed that MBG has the effect of promoting cell proliferation of liver tissues after PH surgery. © 2015 Medicalhelplines.com Inc and John Wiley & Sons Ltd.

Hsieh, M. J., Tang, S. C., Ko, P. C., Chiang, W. C., Tsai, L. K., Chang, A. M., et al. (2015). Improved performance of new prenotification criteria for acute stroke patients. *Journal of the Formosan Medical Association = Taiwan Yi Zhi*,  
BACKGROUND/PURPOSE: We aim to evaluate the accuracy of the new prehospital notification criteria for patients with potential acute stroke in the prehospital setting. METHODS: We conducted a retrospective observational study from March 2011 to February 2013 of potential acute stroke patients prenotified using the new criteria which were: (1) positive Cincinnati Prehospital Stroke Scale (CPSS); (2) symptom onset within 3 hours; and (3) blood glucose level

> 60 mg/dL. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the new criteria were calculated and outcomes of acute stroke patients were reported. Data of all patients with stroke or transient ischemic attack (TIA) transported to the destination hospital were also obtained to evaluate the compliance of emergency medical technicians. RESULTS: There were 2888 patients suspected of stroke by emergency medical technicians and 221 patients prenotified due to meeting the criteria. The PPV, NPV, sensitivity, and specificity of the new criteria were 76.9%, 96.6%, 64.9%, and 98.1%, respectively. Onset time > 3 hours (24/51, 47.1%) and seizure (27.5%) were the two most common conditions leading to false prenotification. Of all prenotified patients, 23.1% (51/221) received thrombolytic therapy. Hemorrhagic stroke or ischemic stroke with hemorrhagic transformation (53.8%) and minor symptoms or rapid recovery (26.9%) were the most common reasons excluding correctly prenotified patients from thrombolytic therapy. CONCLUSION: The accuracy of the new prehospital stroke criteria has higher PPV and specificity compared to previous CPSS validation studies.

Hullender Rubin, L. E., Opsahl, M. S., Wiemer, K. E., Mist, S. D., & Caughey, A. B. (2015). Impact of whole systems traditional chinese medicine on in vitro fertilization outcomes. *Reproductive BioMedicine Online*,

Patients undergoing IVF may receive either acupuncture or whole-systems traditional Chinese medicine (WS-TCM) as an adjuvant IVF treatment. WS-TCM is a complex intervention that can include acupuncture, Chinese herbal medicine, dietary, lifestyle recommendations. In this retrospective cohort study, 1231 IVF patient records were reviewed to assess the effect of adjuvant WS-TCM on IVF outcomes compared among three groups: IVF with no additional treatment; IVF and elective acupuncture on day of embryo transfer; or IVF and elective WS-TCM. The primary outcome was live birth. Of 1069 non-donor cycles, WS-TCM was associated with greater odds of live birth compared with IVF alone (adjusted odds ratio [AOR] 2.09; 95% confidence interval [CI] 1.36 to 3.21), or embryo transfer with acupuncture only (AOR 1.62; 95% CI 1.04 to 2.52). Of 162 donor cycles, WS-TCM was associated with increased live births compared with all groups (odds Ratio [OR] 3.72; 95% CI 1.05 to 13.24, unadjusted) or embryo transfer with acupuncture only (OR 4.09; 95% CI: 1.02 to 16.38, unadjusted). Overall, IVF with

adjuvant WS-TCM was associated with greater odds of live birth in donor and non-donor cycles. These results should be taken cautiously as more rigorous research is needed. © 2015 Reproductive Healthcare Ltd.

Hunsberger, M., McGinnis, P., Smith, J., Beamer, B. A., & O'Malley, J. (2015). Calorie labeling in a rural middle school influences food selection: Findings from community-based participatory research. *Journal of Obesity, 2015*, 531690.

Background. Calorie labeling at the point-of-purchase in chain restaurants has been shown to reduce energy intake. Objective. To investigate the impact of point-of-purchase calorie information at one rural middle school. Methods. With a community-based participatory research framework a mixed method approach was used to evaluate the impact of point-of-purchase calorie information. Students in grades 6-8, dining at the school cafeteria January and February 2010, participated for 17 school days each month; in January a menu was offered in the usual manner without calorie labels; the same menu was prepared in February with the addition of calorie labels at point-of-purchase. Gross calories served per student were measured each day allowing for matched comparison by menu. In March/April of 2010, 32 students who ate in the cafeteria 3 or more times per week were interviewed regarding their views on menu labeling. Results. Calorie consumption decreased by an average of 47 calories/day; fat intake reduced by 2.1 grams/day. Five main themes were consistent throughout the interviews. Conclusion. Point-of-purchase calorie labels can play a role in reducing the number of calories consumed by middle school age children at the lunch. The majority of students interviewed found the calorie labels helped them choose healthier food.

Hunter, J. G. (2015). Achalasia: A to Z. *World Journal of Surgery,*

Hunter, J. G. (2015). Antireflux surgery for dysplastic barrett's esophagus. *Presentations from the 9th Annual Electric Utilities Environmental Conference, 39(3), 595-596.*

Iwasaki, L. R., Covell, D. A., Jr, Frazier-Bowers, S. A., Kapila, S., Huja, S. S., & Nickel, J. C. (2015). Personalized and precision orthodontic therapy. *Orthodontics and Craniofacial Research, 18(S1), 1-7.*

Objective: To bring together orthodontic stakeholders from academics, industry, and private practice for a series of thematically focused workshops to explore and develop the transfer of novel approaches into clinical orthodontic practice. Setting and sample population: Twenty-seven invited speakers, eight poster presenters, and participants of the Consortium for Orthodontic Advances in Science and Technology (COAST) 2014 Innovators' Workshop at the Eaglewood Resort and Spa, Itasca, Illinois, September 11-14, 2014. Material and methods: Five themed sessions involving between 4-7 presentations followed by panel discussions were organized. The aims of the discussion sessions were to highlight important findings and consider the strength of evidence for these, indicate next steps and needed research or technological developments to move forward, and to weigh the expected benefits from these findings and steps to implement in clinical practice. Results: Among important areas for attention identified were need for multiscale and multispecies modeling and experimentation for interspecies translation of results; large-scale collaborative efforts within the profession to address the need for adequate sample sizes for future genetic studies of complex traits such as malocclusion; a consortium approach to improve new technologies such as intra-oral scanning and 3D imaging by establishing standards; and harnessing the growing body of knowledge about bone biology for application in orthodontics. Conclusions: With increased awareness of the potential of current and emerging technologies, translation of personalized and precision approaches in the field of orthodontics holds ever-increasing promise. © 2015 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Jacobson, T. A., Ito, M. K., Maki, K. C., Orringer, C. E., Bays, H. E., Jones, P. H., et al. (2015).

National lipid association recommendations for patient-centered management of dyslipidemia: Part 1-full report. *Journal of Clinical Lipidology*,

The leadership of the National Lipid Association convened an Expert Panel to develop a consensus set of recommendations for patient-centered management of dyslipidemia in clinical medicine. An Executive Summary of those recommendations was previously published. This document provides support for the recommendations outlined in the Executive Summary. The major conclusions include (1) an elevated level of cholesterol carried by circulating apolipoprotein B-containing lipoproteins (non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol [LDL-C], termed atherogenic cholesterol) is a root cause of atherosclerosis, the key underlying

process contributing to most clinical atherosclerotic cardiovascular disease (ASCVD) events; (2) reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies; (3) the intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event; (4) atherosclerosis is a process that often begins early in life and progresses for decades before resulting a clinical ASCVD event. Therefore, both intermediate-term and long-term or lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies; (5) for patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk; (6) nonlipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus; and (7) the measurement and monitoring of atherogenic cholesterol levels remain an important part of a comprehensive ASCVD prevention strategy. © 2015 National Lipid Association.

Jana, J. P. -, Megan, S. O., Emily, S. W., Amalia, M. -. M. L. S., Glen, W., Drum, C. E., et al. (2014). Clinical preventive service use disparities among subgroups of people with disabilities: A scoping review. *Disability and Health Journal*, 7(4), 373-393.

Background: Recommended use of clinical preventive services (CPS) reduces morbidity and mortality from preventable conditions. Disparities in CPS utilization between individuals with and without disabilities have been shown, but a greater understanding of the disability subpopulations with lowest utilization is needed to better inform research, policy, and practice. Objective: The objective was to conduct a scoping review of the literature to identify relevant studies on disparities in receipt of CPS among subgroups of individuals with disabilities. Methods: In July 2010, electronic and manual literature searches were conducted for years 2000-2009. Review for inclusion/exclusion and data analysis occurred in 2010 and 2011. In 2012, the review was updated to cover abstracts published in 2010 and 2011. Identified abstracts, and then full-text articles of included abstracts, were reviewed according to inclusion/exclusion criteria by multiple reviewers. For articles meeting all criteria, two reviewers performed independent data extraction. A gap analysis was performed to identify areas of concentration and gaps in the literature.

Results: Twenty-seven articles met inclusion criteria for this review. Studies varied substantially in sample composition and research methods. CPS examined most often were cervical cancer screening (14 studies) and mammography (13 studies). Potential disparity factors studied most often were disability factors (i.e., disabling condition in 12 studies, disability severity in 10 studies). Stratification of CPS by disparity factors revealed substantial gaps in the literature. Conclusions: The literature gaps point to a need for high quality research on access disparities among subgroups of individuals with disabilities. © 2014 Elsevier Inc. All rights reserved.

Jefferson, J., Thompson, C., Hinshaw, M., & Rich, P. (2015). Coral contact dermatitis. *Dermatology Online Journal*, 21(4)

Corals can elicit both toxic and allergic reactions upon contact with the skin. Clinical presentations vary depending on whether the reaction is acute, delayed, or chronic. Literature concerning cutaneous reactions to corals and other Cnidarians is scarce. Herein we report a case of delayed contact hypersensitivity reaction to coral and review the clinical and histopathological features of coral contact dermatitis. 2015 by the article author(s)

Jia, Y., Bailey, S. T., Hwang, T. S., McClintic, S. M., Gao, S. S., Pennesi, M. E., et al. (2015).

Quantitative optical coherence tomography angiography of vascular abnormalities in the living human eye. *Proceedings of the National Academy of Sciences of the United States of America*, Retinal vascular diseases are important causes of vision loss. A detailed evaluation of the vascular abnormalities facilitates diagnosis and treatment in these diseases. Optical coherence tomography (OCT) angiography using the highly efficient split-spectrum amplitude decorrelation angiography algorithm offers an alternative to conventional dye-based retinal angiography. OCT angiography has several advantages, including 3D visualization of retinal and choroidal circulations (including the choriocapillaris) and avoidance of dye injection-related complications. Results from six illustrative cases are reported. In diabetic retinopathy, OCT angiography can detect neovascularization and quantify ischemia. In age-related macular degeneration, choroidal neovascularization can be observed without the obscuration of details caused by dye leakage in conventional angiography. Choriocapillaris dysfunction can be detected in the nonneovascular form of the disease, furthering our understanding of pathogenesis. In choroideremia, OCT's

ability to show choroidal and retinal vascular dysfunction separately may be valuable in predicting progression and assessing treatment response. OCT angiography shows promise as a noninvasive alternative to dye-based angiography for highly detailed, in vivo, 3D, quantitative evaluation of retinal vascular abnormalities.

Johnson, L. A., Zuloaga, D. G., Bidiman, E., Marzulla, T., Weber, S., Wahbeh, H., et al. (2015). ApoE2 exaggerates PTSD-related behavioral, cognitive and neuroendocrine alterations.

*Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology,*

Apolipoprotein E (apoE) is an essential component of lipoprotein particles in both the brain and periphery, and exists in three isoforms in the human population: E2, E3, and E4. ApoE has numerous, well established roles in neurobiology. Most notably, E4 is associated with earlier onset and increased risk of Alzheimer's disease (AD). While possession of E2 is protective in the context of AD, E2 appears to confer an increased incidence and severity of posttraumatic stress disorder (PTSD). However, the biological processes underlying this link remain unclear. In this study, we began to elucidate these associations by examining the effects of apoE on PTSD severity in combat veterans, and on PTSD-like behavior in mice with human apoE. In a group of 92 veterans with PTSD, we observed significantly higher Clinician Administered PTSD Scale (CAPS) and PTSD checklist (PCL) scores in E2+ individuals, as well as alterations in salivary cortisol levels. Furthermore, we measured behavioral and biological outcomes in mice expressing human apoE after a single stressful event as well as following a period of chronic variable stress, a model of combat-related trauma. Mice with E2 showed impairments in fear extinction, and behavioral, cognitive and neuroendocrine alterations following trauma. To the best of our knowledge, these data constitute the first translational demonstration of PTSD severity in men and PTSD-like symptoms in mice with E2, and point to apoE as a novel biomarker of susceptibility, and potential therapeutic target, for PTSD. *Neuropsychopharmacology* accepted article preview online, 10 April 2015. doi:10.1038/npp.2015.95.

Kain, Z. N., Fitch, J. C., Kirsch, J. R., Mets, B., & Pearl, R. G. (2015). Future of anesthesiology is perioperative medicine: A call for action. *Anesthesiology,*

Kamihara, J., Nyborn, J. A., Olcese, M. E., Nickerson, T., & Mack, J. W. (2015). Parental hope for children with advanced cancer. *Pediatrics*, *135*(5), 868-874.

**BACKGROUND:** Previous work suggests that parents of children with cancer can remain hopeful despite receiving prognostic information, but we know little about what hope means to such parents, or the extent to which parents can feel hopeful even while facing the child's impending death. **METHODS:** We audiotaped conversations between clinicians and parents of 32 children with relapsed or refractory cancer, and then interviewed parents about their hopes and expectations for their child. **RESULTS:** Parent statements about prognosis in interviews mirrored those made by clinicians during discussions about the child's diagnosis with refractory or relapsed cancer. Clinicians used language referring to hope during these conversations but did not ask parents directly about their hopes. Parents expressed a range of hopes for their children, from hopes related to cure or treatment response, to quality of life, normalcy, and love and relationships for the child. For most parents, expectations about prognosis were not aligned with their hopes for the child; for example, many parents hoped for a cure and also reported that they did not believe cure was possible. Many parents were able to acknowledge this incongruence. **CONCLUSIONS:** Parents accurately conveyed the reality of their child's serious condition in the setting of advanced cancer, and yet maintained hope. Hopes were not limited to hope for cure/treatment response. Clinicians should be encouraged to engage in direct conversations about hope with parents as a means to elicit realistic hopes that can help to focus the most meaningful plans for the child and family.

Kelley, R. K., Magbanua, M. J., Butler, T. M., Collisson, E. A., Hwang, J., Sidiropoulos, N., et al. (2015). Circulating tumor cells in hepatocellular carcinoma: A pilot study of detection, enumeration, and next-generation sequencing in cases and controls. *BMC Cancer*, *15*, 206-015-1195-z.

**BACKGROUND:** Circulating biomarkers are urgently needed in hepatocellular carcinoma (HCC). The aims of this study were to determine the feasibility of detecting and isolating circulating tumor cells (CTCs) in HCC patients using enrichment for epithelial cell adhesion molecule (EpCAM) expression, to examine their prognostic value, and to explore CTC-based DNA sequencing in metastatic HCC patients compared to a control cohort with non-malignant liver

diseases (NMLD). METHODS: Whole blood was obtained from patients with metastatic HCC or NMLD. CTCs were enumerated by CellSearch then purified by immunomagnetic EpCAM enrichment and fluorescence-activated cell sorting. Targeted ion semiconductor sequencing was performed on whole genome-amplified DNA from CTCs, tumor specimens, and peripheral blood mononuclear cells (PBMC) when available. RESULTS: Twenty HCC and 10 NMLD patients enrolled. CTCs  $\geq 2/7.5$  mL were detected in 7/20 (35%, 95% confidence interval: 12%, 60%) HCC and 0/9 eligible NMLD ( $p = 0.04$ ). CTCs  $\geq 1/7.5$  mL was associated with alpha-fetoprotein  $\geq 400$  ng/mL ( $p = 0.008$ ) and vascular invasion ( $p = 0.009$ ). Sequencing of CTC DNA identified characteristic HCC mutations. The proportion with  $\geq 100x$  coverage depth was lower in CTCs (43%) than tumor or PBMC (87%) ( $p < 0.025$ ). Low frequency variants were higher in CTCs ( $p < 0.001$ ). CONCLUSIONS: CTCs are detectable by EpCAM enrichment in metastatic HCC, without confounding false positive background from NMLD. CTC detection was associated with poor prognostic factors. Sequencing of CTC DNA identified known HCC mutations but more low-frequency variants and lower coverage depth than FFPE or PBMC.

Kent Anger, W., Elliot, D. L., Bodner, T., Olson, R., Rohlman, D. S., Truxillo, D. M., et al. (2015). Effectiveness of total worker health interventions. *Journal of Occupational Health Psychology*, 20(2), 226-247.

Total Worker Health (TWH) was introduced and the term was trademarked in 2011 by the National Institute for Occupational Safety and Health (NIOSH) to formally signal the expansion of traditional occupational safety and health (OSH) to include wellness and well-being. We searched PubMed, PsycInfo, and other databases using keywords TWH, health promotion, health protection, and variants for articles meeting the criteria of (a) employing both occupational safety and/or health (OSH, or health protection) and wellness and/or well-being (health promotion, or HP) in the same intervention study, and (b) reporting both OSH and HP outcomes. Only 17 published studies met these criteria. All but 1 of the 17 TWH interventions improved risk factors for injuries and/or chronic illnesses, and 4 improved 10 or more risk factors. Several TWH interventions reported sustained improvements for over a year, although only 1 is readily available for dissemination. These results suggest that TWH interventions that address both injuries and chronic diseases can improve workforce health effectively and more rapidly than the

alternative of separately employing more narrowly focused programs to change the same outcomes in serial fashion. These 17 articles provide useful examples of how TWH interventions can be structured. The promise of simultaneous improvements in safety, health, and well-being leads to the call to pursue TWH research to identify and disseminate best practices. © 2014 American Psychological Association.

Kesselheim, J. C., Atlas, M., Adams, D., Aygun, B., Barfield, R., Eisenman, K., et al. (2015).

Humanism and professionalism education for pediatric hematology-oncology fellows: A model for pediatric subspecialty training. *Pediatric Blood and Cancer*, 62(2), 335-340.

Humanism and professionalism are virtues intrinsic to the practice of medicine, for which we lack a standard, evidence-based approach for teaching and evaluation. Pediatric hematology-oncology (PHO) fellowship training brings new and significant stressors, making it an attractive setting for innovation in humanism and professionalism training. Procedure: We electronically surveyed a national sample of PHO fellows to identify fellows' educational needs in humanism and professionalism. Next, we developed a case-based, faculty-facilitated discussion curriculum to teach this content within pilot fellowship programs. We assessed whether fellowships would decide to offer the curriculum, feasibility of administering the curriculum, and satisfaction of fellow and faculty participants. Results: Surveys were completed by 187 fellows (35%). A minority (29%) reported that their training program offers a formal curriculum in humanism and/or professionalism. A majority desires more formal teaching on balancing clinical practice and research (85%), coping with death/dying (85%), bereavement (78%), balancing work and personal life (75%), navigating challenging relationships with patients (74%), and depression/burn out (71%). These six topics were condensed into four case-based modules, which proved feasible to deliver at all pilot sites. Ten fellowship programs agreed to administer the novel curriculum. The majority (90%) of responding fellows and faculty reported the sessions touched on issues important for training, stimulated reflective communication, and were valuable. Conclusions: Pediatric hematology-oncology fellows identify numerous gaps in their training related to humanism and professionalism. This curriculum offers an opportunity to systematically address these educational needs and can serve as a model for wider implementation. © 2014 Wiley Periodicals, Inc.

Khvostenko, D., Salehi, S., Naleway, S. E., Hilton, T. J., Ferracane, J. L., Mitchell, J. C., et al. (2015).

Cyclic mechanical loading promotes bacterial penetration along composite restoration marginal gaps. *Dental Materials : Official Publication of the Academy of Dental Materials*,

OBJECTIVES: Secondary caries is the most common reason for composite restoration replacement and usually forms between dentin and the filling. The objective of this study was to investigate the combined effect of cyclic loading and bacterial exposure on bacterial penetration into gaps at the interface between dentin and resin composite restorative material using a novel bioreactor system and test specimen design. METHODS: Human molars were machined into 3mm thick disks with 2mm deepx5mm diameter cavity preparations into which composite restorations were placed. A approximately 15-30µm (small) or approximately 300µm wide (large) marginal gap was introduced along half of the interface between the dentin and restoration. Streptococcus mutans UA 159 biofilms were grown on each sample prior to testing each in a bioreactor both with and without cyclic loading. Both groups of samples were tested for 2 weeks and post-test biofilm viability was confirmed with a live-dead assay. Samples were fixed, mounted and cross-sectioned to reveal the gaps and observe the depth of bacterial penetration. RESULTS: It was shown that for large gap samples the bacteria easily penetrated to the full depth of the gap independent of loading or non-loading conditions. The results for all cyclically loaded small gap samples show a consistently deep bacterial penetration down 100% of the gap while the average penetration depth was only 67% for the non-loaded samples with only two of six samples reaching 100%. SIGNIFICANCE: A new bioreactor was developed that allows combining cyclic mechanical loading and bacterial exposure of restored teeth for bacterial biofilm and demineralization studies. Cyclic loading was shown to aid bacterial penetration into narrow marginal gaps, which could ultimately promote secondary caries formation.

Kolivras, A., Thompson, C., Metz, T., & André, J. (2015). Macular arteritis associated with concurrent HIV and hepatitis B infections: A case report and evidence for a disease spectrum association with cutaneous polyarteritis nodosa. *Journal of Cutaneous Pathology*,

We report the first case of macular arteritis in a 33-year-old Black, African female with concurrent human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections. Of particular interest in macular arteritis is the striking discordance between the clinical presentation and the

histopathological findings, a fact that both dermatologists and dermatopathologists should be aware. Histopathologically, the case showed typical findings of macular arteritis with a perivascular, predominantly lymphocytic, infiltrate and intraluminal thrombosis. Both HIV and HBV have been reported as viral inducers of cutaneous polyarteritis nodosa (PAN). Their association with macular arteritis in this case supports existing evidence that macular arteritis and cutaneous PAN represent a single-disease spectrum of vasculitides, with macular arteritis representing the chronic, lymphocytic and indolent stage, and cutaneous PAN the neutrophilic, acute stage with a risk for systemic progression. Lymphocytic thrombophilic arteritis (LTA), a third, uncommon disease would be in between macular arteritis and cutaneous PAN on a spectrum. Features of this case and other published cases provide strong evidence that there is a single, mild-to-severe disease spectrum of macular arteritis-LTA-cutaneous PAN. © 2015 John Wiley & Sons A/S.

Kosoff, R. E., Aslan, J. E., Kostyak, J. C., Dulaimi, E., Chow, H. Y., Prudnikova, T. Y., et al. (2015).

Pak2 restrains endomitosis during megakaryopoiesis and alters cytoskeleton organization. *Blood*, Megakaryocyte maturation and polyploidization are critical for platelet production; abnormalities in these processes are associated with myeloproliferative disorders, including thrombocytopenia. Megakaryocyte maturation signals through cascades that involve p21-activated kinase (Pak) function, however, the specific role for Pak kinases in megakaryocyte biology remains elusive. Here, we identify Pak2 as an essential effector of megakaryocyte maturation, polyploidization and proplatelet formation. Genetic deletion of Pak2 in murine bone marrow is associated with macrothrombocytopenia, altered megakaryocyte ultrastructure, increased bone marrow megakaryocyte precursors and an elevation of mature CD41<sup>+</sup>-megakaryocytes, as well as an increased number of polyploid cells. In Pak2<sup>-/-</sup> mice, platelet clearance rate was increased, as was production of newly synthesized, reticulated platelets. In vitro, Pak2<sup>-/-</sup> megakaryocytes demonstrate increased polyploidization associated with alterations in beta1-tubulin expression and organization, decreased proplatelet extensions and reduced phosphorylation of the endomitosis regulators LIMK, cofilin, and Aurora A/B/C. Together, these data establish a novel role for Pak2 as an important regulator of megakaryopoiesis, polyploidization and cytoskeletal dynamics in developing megakaryocytes.

Kramer, P. F., & Williams, J. T. (2015). Cocaine decreases metabotropic glutamate receptor mGluR1 currents in dopamine neurons by activating mGluR5. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, Midbrain dopamine neurons are important mediators of reward and movement and are sensitive to cocaine-induced plasticity. After even a single injection of cocaine, there is an increase in AMPA-dependent synaptic transmission. The present study examines cocaine-induced plasticity of mGluR-dependent currents in dopamine neurons in the substantia nigra. Activation of mGluR1 and mGluR5 resulted in a mixture of inward and outward currents mediated by a nonselective cation conductance and a calcium-activated potassium conductance (SK), respectively. A single injection of cocaine decreased the current activated by mGluR1 in dopamine neurons, and it had no effect on the size of the mGluR5-mediated current. When the injection of cocaine was preceded by treatment of the animals with a blocker of mGluR5 receptors (MPEP), cocaine no longer decreased the mGluR1 current. Thus, the activation of mGluR5 was required for the cocaine-mediated suppression of mGluR1-mediated currents in dopamine neurons. The results support the hypothesis that mGluR5 coordinates a reduction in mGluR1 functional activity after cocaine treatment. *Neuropsychopharmacology advance online publication*, 29 April 2015; doi:10.1038/npp.2015.91.

Kroenke, C. D., Mills, B. D., Olavarria, J. F., & Neil, J. J. (2014). *Neuroanatomy of the ferret brain with focus on the cerebral cortex* Wiley Blackwell.

This chapter discusses the brain anatomy of ferrets (*Mustela putorius furo*). The cerebral cortex of adult ferrets is folded into several gyri and sulci, which makes them an attractive model for studying factors influencing the development and organization of the cortical mantle. The chapter first presents an overview, and then goes on to describe the development of the cerebral cortex. The primary or striate visual cortex (area 17) spans the occipital ridge of the ferret brain across its ventral/lateral to dorsomedial extent. The two primary auditory areas, A1 and AAF, are located on the dorsal-most middle ectosylvian gyrus (MEG). As with other sensory systems, several similarities in the organization of somatosensory cortex have been noted between the ferret and the cat. Numerous regions in the ferret cerebral cortex have been described as having properties of multisensory cortex. © 2014 by John Wiley & Sons, Inc.

Kuang, A., & Selden, N. R. (2015). Secondary cranial vault remodeling for restenosis after primary sagittal synostosis repair. *Pediatric Neurosurgery*,

The mainstay of treatment for single-suture cranial synostosis is cranial vault reconstruction. After primary cranial vault remodeling, patients are at risk for cranial restenosis and delayed intracranial hypertension, which may result in developmental delay or blindness. Synostosis patients are therefore generally monitored periodically for signs and symptoms of intracranial hypertension that may indicate a second cranial expansion procedure. The authors present a carefully illustrated case of a patient who presented 2 years after primary cranial vault reconstruction for sagittal synostosis with a decrease in head circumference percentile, recurrent cranial dysmorphism, papilledema, headaches and computed tomographic imaging findings consistent with cranial restenosis. These findings resolved after secondary cranial vault remodeling. The authors advocate a protocol of prospective routine clinical and radiographic follow-up after primary cranial vault repair for single-suture cranial synostosis, and illustrate the specific clinical and radiographic findings suggestive of this late complication in a representative individual patient. (c) 2015 S. Karger AG, Basel.

Kuehl, K. S. (2012). *Cherry juice targets antioxidant potential and pain relief* S. Karger AG.

Strenuous physical activity increases the risk of musculoskeletal injury and can induce muscle damage resulting in acute inflammation and decreased performance. The human body's natural response to injury results in inflammation-induced pain, swelling, and erythema. Among sports medicine physicians and athletic trainers, the mainstays of urgent treatment of soft tissue injury are rest, ice, compression, and elevation (RICE). In order to reduce pain and inflammation, anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAIDs) act on the multiple inflammatory pathways, which, although often very effective, can have undesirable side effects such as gastric ulceration and, infrequently, myocardial infarction and stroke. For centuries, natural anti-inflammatory compounds have been used to mediate the inflammatory process and often with fewer side effects. Tart cherries appear to possess similar effectiveness in treating the inflammatory reaction seen in both acute and chronic pain syndromes encountered among athletes and non-athletes with chronic inflammatory disease. This article reviews the antioxidant and anti-inflammatory effects of tart cherries on prevention, treatment, and recovery of soft

tissue injury and pain. © 2012 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland). All rights reserved.

Kuppermann, M., Pena, S., Bishop, J. T., Nakagawa, S., Gregorich, S. E., Sit, A., et al. (2015). Effect of enhanced information, values clarification, and removal of financial barriers on use of prenatal genetic testing: A randomized clinical trial. *Obstetrical and Gynecological Survey*, 70(1), 7-9.

Langdahl, B. L., Teglbjærg, C. S., Ho, P. -, Chapurlat, R., Czerwinski, E., Kendler, D. L., et al. (2015). A 24-month study evaluating the efficacy and safety of denosumab for the treatment of men with low bone mineral density: Results from the ADAMO trial. *Journal of Clinical Endocrinology and Metabolism*, 100(4), 1335-1342.

Context: One in 4 men in the United States aged >50 years will have an osteoporosis-related fracture. Fewer data are available on osteoporosis treatment in men than in women. Objective: The purpose of this study was to evaluate denosumab therapy in men with low bone mineral density (BMD). Design: This was a phase 3 study with 2 treatment periods: a previously reported 12-month doubleblind, placebo-controlled phase and a 12-month open-label phase. Setting: This was a multicenter study conducted in North America and Europe. Participants: A total of 228 men entered the open-label phase and 219 completed the study. Intervention: Men from the original denosumab (long-term) and placebo (crossover) groups received 60 mg of denosumab sc every 6 months. Main Outcome Measures: BMD, serum collagen type I C-telopeptide, and safety were measured. Results: During the open-label phase, continued BMD increases occurred with long-term denosumab treatment (2.2% lumbar spine, 0.9% total hip, 1.3% femoral neck, 1.3% trochanter, and 0.2% 1/3 radius), resulting in cumulative 24-month gains from baseline of 8.0%, 3.4%, 3.4%, 4.6%, and 0.7%, respectively (all P <01). The crossover group showed BMD gains after 12 months of denosumab treatment similar to those of the long-term denosumab group during the first treatment year. Significant reductions in serum collagen type I C-telopeptide were observed after denosumab administration. Adverse event rates were similar between groups, and no new safety signals were identified. Conclusions: In men with low BMD, denosumab treatment for a second year continued to increase BMD, maintained reductions in bone resorption, and was well tolerated. BMD increased in men initiating denosumab during the

second year. These effects were similar to those previously seen in postmenopausal women with osteoporosis and in men with prostate cancer receiving androgen deprivation therapy. Copyright © 2015 by the Endocrine Society.

Lavotshkin, S., Jalas, J. R., Torisu-Itakura, H., Ozao-Choy, J., Lee, J. H., Sim, M. S., et al. (2015).

Immunoprofiling for prognostic assessment of colon cancer: A novel complement to ultrastaging. *Journal of Gastrointestinal Surgery*,

Background: Although AJCC/TNM staging remains the gold standard for prognostic assessment of colon cancer, stage-specific outcomes vary. We therefore prospectively evaluated the prognostic role of immunoprofiling. Methods: Our cohort included 35 patients from an ongoing prospective trial of ultrastaging for colon cancer. Specimens were analyzed for T cell markers (CD3, CD4, CD8, and FoxP3). The number of tumor-infiltrating lymphocytes was analyzed at the tumor's margin and center and correlated with AJCC/TNM stage, clinicopathologic variables, and disease-free survival. Results: There was a significant inverse association between number of CD3+ cells in the tumor center and tumor stage ( $P = 0.05$ ). The tumor center/margin ratio of CD3+ cells also showed an inverse but non-significant relationship with nodal involvement ( $P = 0.07$ ). Body mass index was inversely associated with numbers of CD3+ ( $P = 0.04$ ) and CD8+ ( $P = 0.02$ ) cells. Longer disease-free survival was correlated with higher CD8+ counts ( $P = 0.07$ ), lower CD4+/CD8+ ratios ( $P = 0.008$ ), and higher CD8+/FoxP3+ ratios ( $P = 0.02$ ). Conclusions: This is the first prospective validation of immunoprofiling in patients whose colon cancer is staged with strict surgical and pathology quality measures. The apparent correlation between immunophenotypic response and clinical outcome warrants evaluation in a larger prospective trial. © 2015 The Society for Surgery of the Alimentary Tract

Lee, J. J., Protheroe, C. A., Luo, H., Ochkur, S. I., Scott, G. D., Zellner, K. R., et al. (2015).

Eosinophil-dependent skin innervation and itching following contact toxicant exposure in mice. *The Journal of Allergy and Clinical Immunology*, 135(2), 477-487.

BACKGROUND: Contact toxicant reactions are accompanied by localized skin inflammation and concomitant increases in site-specific itch responses. The role(s) of eosinophils in these reactions is poorly understood. However, previous studies have suggested that localized eosinophil-nerve

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

Li, H., Kachelmeier, A., Furness, D. N., & Steyger, P. S. (2015). Local mechanisms for loud sound-enhanced aminoglycoside entry into outer hair cells. *Frontiers in Cellular Neuroscience*, 9(APR)

Loud sound exposure exacerbates aminoglycoside ototoxicity, increasing the risk of permanent hearing loss and degrading the quality of life in affected individuals. We previously reported that loud sound exposure induces temporary threshold shifts (TTS) and enhances uptake of aminoglycosides, like gentamicin, by cochlear outer hair cells (OHCs). Here, we explore mechanisms by which loud sound exposure and TTS could increase aminoglycoside uptake by OHCs that may underlie this form of ototoxic synergy. Mice were exposed to loud sound levels to induce TTS, and received fluorescently-tagged gentamicin (GTTR) for 30 min prior to fixation. The degree of TTS was assessed by comparing auditory brainstem responses (ABRs) before and after loud sound exposure. The number of tip links, which gate the GTTR-permeant

mechanoelectrical transducer (MET) channels, was determined in OHC bundles, with or without exposure to loud sound, using scanning electron microscopy. We found wide-band noise (WBN) levels that induce TTS also enhance OHC uptake of GTTR compared to OHCs in control cochleae. In cochlear regions with TTS, the increase in OHC uptake of GTTR was significantly greater than in adjacent pillar cells. In control mice, we identified stereociliary tip links at ~50% of potential positions in OHC bundles. However, the number of OHC tip links was significantly reduced in mice that received WBN at levels capable of inducing TTS. These data suggest that GTTR uptake by OHCs during TTS occurs by increased permeation of surviving, mechanically-gated MET channels, and/or non-MET aminoglycoside-permeant channels activated following loud sound exposure. Loss of tip links would hyperpolarize hair cells and potentially increase drug uptake via aminoglycoside-permeant channels expressed by hair cells. The effect of TTS on aminoglycoside-permeant channel kinetics will shed new light on the mechanisms of loud sound-enhanced aminoglycoside uptake, and consequently on ototoxic synergy. © 2015 Li, Kachelmeier, Furness and Steyger.

Lim, A., Shin, K., Zhao, C., Kawano, S., & Beachy, P. A. (2014). Spatially restricted hedgehog signalling regulates HGF-induced branching of the adult prostate. *Nature Cell Biology*, 16(12), 1135-1145.

Branching morphogenesis is thought to be governed by epithelial-stromal interactions, but the mechanisms underlying specification of branch location remain largely unknown. Prompted by the striking absence of Hedgehog (Hh) response at the sites of nascent buds in regenerating tubules of the adult prostate, we investigated the role of Hh signalling in adult prostate branching morphogenesis. We find that pathway activity is localized to stromal cells, and that its attenuation by genetic or pharmacologic manipulation leads to increased branching. Decreased pathway activity correlates with increased stromal production of hepatocyte growth factor (Hgf), and we show that Hgf induces epithelial tubule branching. Regulation of Hgf expression by Hh signalling is indirect, mediated by Hh-induced expression of the microRNAs miR-26a and miR-26b, which in turn downregulate expression of Hgf. Prostate tubule branching thus may be initiated from regions of low Hh pathway activity, with implications for the prostatic hyperplasia commonly observed in late adulthood. © 2014 Macmillan Publishers Limited. All rights reserved.

Little, S. E., & Caughey, A. B. (2015). Induction of labor and cesarean: What is the true relationship? *Clinical Obstetrics and Gynecology*, 58(2), 269-281.

It is a commonly held belief that labor induction increases the risk of cesarean delivery; women who are induced are at higher risk of cesarean as compared with those in spontaneous labor. This comparison group is inaccurate, however, as women and providers cannot choose spontaneous labor as the alternative to labor induction. With expectant management, spontaneous labor may occur, but as gestation advances, pregnancy complications may occur, or women may progress postterm requiring induction at a later gestation. Using the proper comparison group, studies find that labor induction is actually associated with a small decreased risk of cesarean delivery.

Liu, F., Zhang, Z., Zhu, L., & Liu, Y. (2015). Propagation modeling of point source excited magnetoinductive waves based on a new plane wave expansion approach. *Mathematical Problems in Engineering*, 2015

The signal fading in wireless underground sensor networks (WUSNs), which is caused by lossy media such as soil and sand, can be reduced by applying technology of magnetoinductive (MI) propagation. This technology can effectively establish a communication at very low frequency (VLF). In contrast to the previous studies in the literature, which mostly focus on the propagation of plane waves, we propose a new approach based on the plane wave expansion (PWE) to model the near field MI waves. The proposed approach is based on excitation of a point source, which is a common case in a practical WUSN. The frequent usage of square lattice MI structure is investigated. To verify the mathematical derivation, the simulation of time domain based on the fourth-order Runge-Kutta (RK) method is carried out. Simulation results show that the new model can provide a precise prediction to the MI wave's propagation, with the computation load being one-tenth of that of the time domain simulation. The characteristics of the propagation of the MI waves are presented and discussed. Finally, the reflection on the edge of the MI structure is reduced by analysing the terminal matching conditions and calculating a method for matching impedances. © 2015 Feng Liu et al.

Lo, J. O., Shaffer, B. L., Feist, C. D., & Caughey, A. B. (2015). Chromosomal microarray analysis and prenatal diagnosis. *Obstetrical and Gynecological Survey*, 69(10), 613-621.

Chromosomal microarray analysis (CMA) assesses chromosomal copy number alterations and affords higher resolution when compared with standard karyotype. This review provides the obstetric provider with an update on the technology, use, and controversies concerning CMA utilization in prenatal diagnosis. Chromosomal microarray analysis offers increased resolution for copy number abnormalities compared with traditional karyotype. There is high-quality evidence for the added detection of clinically significant copy number alterations with CMA in prenatal diagnosis when the traditional karyotype is normal. Other potential advantages of CMA include a quicker turnaround time and utilization in clinical situations with a high probability of nondividing cells (ie, intrauterine fetal demise, spontaneous miscarriage, and third-trimester amniocentesis). Chromosomal microarray analysis may be beneficial when prenatally detected structural anomalies are associated with specific microdeletions and microduplications or to assess for copy number variants when a de novo balanced rearrangement or marker chromosome is diagnosed. Use of CMA includes the detection of copy number variants of uncertain significance. In light of these issues, large prospective cohort studies are needed to illustrate the diagnostic utility of CMA for detection of prenatal chromosomal abnormalities in low-risk populations before routine clinical use of CMA is recommended in all circumstances of prenatal diagnosis. Target Audience: Obstetricians and gynecologists, family medicine, midwives Learning Objectives: After completing this CME activity, physicians should be better able to compare the use of chromosomal microarray analysis with karyotyping in prenatal diagnostic testing, choose which patients are appropriate candidates for chromosomal microarray analysis, and evaluate the results of chromosomal microarray analysis. Copyright © 2014 Lippincott Williams & Wilkins.

Lombard-Bohas, C., Yao, J. C., Hobday, T., Van Cutsem, E., Wolin, E. M., Panneerselvam, A., et al. (2015). Impact of prior chemotherapy use on the efficacy of everolimus in patients with advanced pancreatic neuroendocrine tumors a subgroup analysis of the phase III RADIANT-3 trial. *Pancreas*, 44(2), 181-189.

Objective: The aim of this study was to evaluate efficacy and safety of everolimus in patients with pancreatic neuroendocrine tumors (pNET) by prior chemotherapy use in the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3). Methods: Patients with advanced, progressive, low- or intermediate-grade pNET were prospectively stratified by prior chemotherapy

use and World Health Organization performance status and were randomly assigned (1:1) to everolimus 10 mg/d (n = 207) or placebo (n = 203). Results: Of the 410 patients, 204 (50%) were naive to chemotherapy (chemonaive). Baseline characteristics were similar for patients with or without prior chemotherapy. Everolimus significantly prolonged median progression-free survival regardless of prior chemotherapy use (prior chemotherapy: 11.0 vs 3.2 months; hazard ratio, 0.34; 95% confidence interval, 0.25A-A0.48; P < 0.0001) (chemonaive: 11.4 vs 5.4 months; hazard ratio, 0.42; 95% confidence interval, 0.29A-A0.60; P < 0.0001). Stable disease was the best overall response in 73% of everolimus-treated patients (151/207). The most common drug-related adverse events included stomatitis (60-69%), rash (47-50%), and diarrhea (34%). Conclusions: As more treatment options become available, it is important to consider the goals of treatment and to identify patients who would potentially benefit from a specific therapy. Findings from this planned subgroup analysis suggest the potential for first-line use of everolimus in patients with advanced pNET. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Loriot, Y., Miller, K., Sternberg, C. N., Fizazi, K., De Bono, J. S., Chowdhury, S., et al. (2015). Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): Results from a randomised, phase 3 trial. *The Lancet.Oncology*,  
BACKGROUND: Enzalutamide significantly increased overall survival and radiographic progression-free survival compared with placebo in the PREVAIL trial of asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer. We report the effect of enzalutamide on health-related quality of life (HRQoL), pain, and skeletal-related events observed during this trial. METHODS: In this phase 3, double-blind trial, patients were randomly assigned (1:1) to receive enzalutamide 160 mg/day (n=872) or placebo (n=845) orally. HRQoL was assessed at baseline and during treatment using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and EQ-5D questionnaires. Pain status was assessed at screening, baseline, week 13, and week 25 with the Brief Pain Inventory Short Form (BPI-SF). The primary analysis of HRQoL data used a mixed-effects model to test the difference between least square means change from baseline at week 61. We assessed change

from baseline, percentage improvement, and time to deterioration in HRQoL and pain, the proportion of patients with a skeletal-related event, and time to first skeletal-related event. Analysis was done on the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01212991. FINDINGS: Median treatment duration was 16.6 months (IQR 10.1-21.1) in the enzalutamide group and 4.6 months (2.8-9.7) in the placebo group. The mixed-effects model analyses showed significant treatment differences in change from baseline to week 61 with enzalutamide compared with placebo for most FACT-P endpoints and EQ-5D visual analogue scale. Median time to deterioration in FACT-P total score was 11.3 months (95% CI 11.1-13.9) in the enzalutamide group and 5.6 months (5.5-5.6) in the placebo groups (hazard ratio [HR] 0.62 [95% CI 0.54-0.72];  $p < 0.0001$ ). A significantly greater proportion of patients in the enzalutamide group than in the placebo group reported clinically meaningful improvements in FACT-P total score (327 [40%] of 826 vs 181 [23%] of 790), in EQ-5D utility index (224 [28%] of 812 vs 99 [16%] of 623), and visual analogue scale (218 [27%] of 803 vs 106 of [18%] 603; all  $p < 0.0001$ ). Median time to progression in BPI-SF pain at its worst was 5.7 months (95% CI 5.6-5.7) in the enzalutamide group and 5.6 months (5.4-5.6) in the placebo group (HR 0.62 [95% CI 0.53-0.74];  $p < 0.0001$ ). Progression of pain at its worst was less common in the enzalutamide group than in the placebo group at week 13 (220 [29%] of 769 vs 257 [42%] of 610;  $p < 0.0001$ ), but not at week 25 (225 [32%] of 705 vs 135 [38%] of 360;  $p = 0.068$ ). 278 (32%) of 872 patients in the enzalutamide group and 309 (37%) of 845 patients in the placebo group had experienced a skeletal-related event by data cutoff. Median time to first skeletal-related events in the enzalutamide group was 31.1 months (95% CI 29.5-not reached) and 31.3 months (95% CI 23.9-not reached) in the placebo group (HR 0.72 [95% CI 0.61-0.84];  $p < 0.0001$ ). INTERPRETATION: In addition to improving overall survival relative to placebo, enzalutamide significantly improves patient-related outcomes and delays occurrence of first skeletal-related event in chemotherapy-naive men with metastatic castration-resistant prostate cancer. FUNDING: Astellas Pharma and Medivation.

Macdonald, C. M., Jacques, S. L., & Meglinski, I. V. (2015). Circular polarization memory in polydisperse scattering media. *Physical Review.E, Statistical, Nonlinear, and Soft Matter Physics*, 91(3-1), 033204.

We investigate the survival of circularly polarized light in random scattering media. The surprising persistence of this form of polarization has a known dependence on the size and refractive index of scattering particles, however a general description regarding polydisperse media is lacking. Through analysis of Mie theory, we present a means of calculating the magnitude of circular polarization memory in complex media, with total generality in the distribution of particle sizes and refractive indices. Quantification of this memory effect enables an alternate pathway toward recovering particle size distribution, based on measurements of diffusing circularly polarized light.

Madsen, R. J., Chim, J., Ang, B., Fisher, O., & Hansen, J. (2015). Variance in the origin of the pectoralis major muscle: Implications for implant-based breast reconstruction. *Annals of Plastic Surgery*, 74(1), 111-113.

Background: The pectoralis major muscle plays a crucial role in implantbased breast reconstruction. The goal of this study is to document variations of the origin of the pectoralis major muscle (PM). We hope to understand how many women have anatomy allowing for total submuscular coverage of an implant with the PM alone in immediate breast reconstruction.

Methods: Fifty patients undergoing mastectomy were recruited. Breast width and the costal origin of the natural inframammary fold (IMF) were measured preoperatively and intraoperatively. The PM width at its origin and the rib origin of the PM were measured intraoperatively. A ratio of the PM origin width to breast width was calculated. Results: Forty-four percent of breasts studied had the IMF at the level of the seventh rib, 53% at the sixth rib, and 3% at the fifth rib. Twenty percent of PM muscles originated from the seventh rib, 68% from the sixth rib, and 12% from the fifth rib. Thirty-six percent of chests showed a PM originating one rib level above the IMF, 61% at the same level, and 3% one level below the IMF. Seventy-seven percent of chests showed a PM origin width to breast width ratio of  $<0.8$ . Conclusions: Overall, 72% of chests had either a high origin of the PM, a narrow PM relative to the breast width, or both. This anatomy is suboptimal for implant coverage using the PM alone. Surgeons performing implant-based breast reconstruction should be prepared to utilize wide dissection, alternative muscle recruitment, or supplemental acellular dermal matrix. Copyright © 2013 by Lippincott Williams & Wilkins.

Maire, J. J., Close, L. N., Heinricher, M. M., & Selden, N. R. (2015). Distinct pathways for norepinephrine- and opioid-triggered antinociception from the amygdala. *European Journal of Pain (London, England)*,

BACKGROUND: The amygdala has an important role in pain and pain modulation. We showed previously in animal studies that alpha2 -adrenoreceptor activation in the central nucleus of the amygdala (CeA) mediates hypoalgesia produced by restraint stress, and that direct application of an alpha2 -agonist in this region produces analgesia. AIMS: In the present animal experiments, we investigated the pathways through which alpha2 -sensitive systems in the CeA produce behavioural analgesia. The CeA has dense connections to a descending pain modulatory network, centred in the midbrain periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM), which is implicated in various forms of stress-related hypoalgesia and which mediates the antinociceptive effect of morphine applied in the basolateral amygdala. We investigated whether this circuit mediates the hypoalgesic effects of alpha2 -adrenergic agonist administration into the CeA as well as the contribution of endogenous opioids and cannabinoids. We also tested the possibility that activation of alpha2 -receptors in the CeA produces antinociception by recruitment of noradrenergic pathways projecting to the spinal cord. RESULTS: Hypoalgesia resulting from bilateral application of the alpha2 -adrenergic agonist clonidine in the CeA was not reversed by chemical inactivation of the RVM or by systemic injections of naloxone (mu-opioid antagonist) or rimonabant (CB1 antagonist). By contrast, spinal alpha2 -receptor blockade (intrathecal idazoxan) completely prevented the hypoalgesic effect of clonidine in the CeA, and unmasked a small but significant hyperalgesia. CONCLUSION: In rats, adrenergic actions in the CeA mediating hypoalgesia require spinal adrenergic neurotransmission but not the PAG-RVM pain modulatory network, or opiate or cannabinoid systems.

Malhotra, R., Turner, K., Sonnenberg, A., & Genta, R. M. (2015). High prevalence of inflammatory bowel disease in united states residents of indian ancestry. *Clinical Gastroenterology and Hepatology*, 13(4), 683-689.

Background and Aims: It is unclear whether the reported low prevalence of inflammatory bowel disease (IBD) in Southern and Eastern Asia is real (caused by genetic or environmental factors) or spurious (because of differences in awareness of the condition among physicians or different

interpretations of endoscopic and histologic features). We aimed to estimate the prevalence of IBD in patients of different ethnicities who underwent endoscopy in the United States, with ileocolonic biopsies evaluated by a single group of gastrointestinal pathologists. Methods: We used a national pathology database to collect data on 1,027,977 subjects who underwent colonoscopy with ileocolonic biopsies from January 2008 through December 2013 throughout the United States; mucosal biopsy specimens were evaluated and reported by 1 group of 35 histopathologists. Patients were stratified into the following ancestries: Indian (persons with ancestry in the Indian subcontinent), East Asian (China, Korea, Japan, and Vietnam), Hispanic, Jewish, and Other. The prevalence of ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis was determined for each ethnic group. Results: In the study population, 30,812 patients were diagnosed with IBD (20,308 with UC, 7706 with CD, and 2798 with indeterminate colitis). UC was more commonly associated with Indian and Jewish ethnicity and less commonly associated with East Asian and Hispanic ethnicity. Similar patterns also applied to CD and to all types of IBD analyzed jointly. Among Indian patients, 11.7% of those of Gujarati origins had IBD, compared with 7.9% of other Indians (odds ratio, 1.5; 95% confidence interval, 1.14-2.11). Conclusions: Patients of Indian origin living in the United States have a greater risk for all types of IBD than other American populations. East Asians and Hispanics have a lower risk, possibly similar to that of the populations still living in their original countries. These findings may have relevance to the practice of gastroenterology in countries where there are sizable portions of the population with roots in the Indian subcontinent. © 2015 AGA Institute.

Marijon, E., Uy-Evanado, A., Reinier, K., Teodorescu, C., Narayanan, K., Jouven, X., et al. (2015).

Sudden cardiac arrest during sports activity in middle age. *Circulation*, 131(16), 1384-1391.

BACKGROUND: Sports-associated sudden cardiac arrests (SCAs) occur mostly during middle age.

We sought to determine the burden, characteristics, and outcomes of SCA during sports among middle-aged residents of a large US community. METHODS AND RESULTS: Patients with SCA who were 35 to 65 years of age were identified in a large, prospective, population-based study (2002-2013), with systematic and comprehensive assessment of their lifetime medical history. Of the 1247 SCA cases, 63 (5%) occurred during sports activities at a mean age of 51.1+/-8.8 years, yielding an incidence of 21.7 (95% confidence interval, 8.1-35.4) per 1 million per year. The

incidence varied significantly by sex, with a higher incidence among men (relative risk, 18.68; 95% confidence interval, 2.50-139.56) for sports SCAs compared with all other SCAs (relative risk 2.58; 95% confidence interval, 2.12-3.13). Sports SCA was also more likely to be a witnessed event (87% versus 53%;  $P=1$  cardiovascular risk factors in 56%, and overall, 36% of cases had typical cardiovascular symptoms during the week preceding the SCA. CONCLUSIONS: Sports-associated SCA in middle age represents a relatively small proportion of the overall SCA burden, reinforcing the idea of the high-benefit, low-risk nature of sports activity. Especially in light of current population aging trends, our findings emphasize that targeted education could maximize both safety and acceptance of sports activity in the older athlete.

Marinko, M., Novakovic, A., Nenezic, D., Stojanovic, I., Milojevic, P., Jovic, M., et al. (2015).

Nicorandil directly and cyclic GMP-dependently opens K channels in human bypass grafts. *Journal of Pharmacological Sciences*,

As we previously demonstrated the role of different K<sup>+</sup> channels in the action of nicorandil on human saphenous vein (HSV) and human internal mammary artery (HIMA), this study aimed to analyse the contribution of the cGMP pathway in nicorandil-induced vasorelaxation and to determine the involvement of cGMP in the K<sup>+</sup> channel-activating effect of nicorandil. An inhibitor of soluble guanylate cyclase (GC), ODQ, significantly inhibited nicorandil-induced relaxation, while ODQ plus glibenclamide, a selective ATP-sensitive K<sup>+</sup> (KATP) channel inhibitor, produced a further inhibition of both vessels. In HSV, ODQ in combination with 4-aminopyridine, a blocker of voltage-gated K<sup>+</sup> (KV) channels, did not modify the concentration-response to nicorandil compared with ODQ, whereas in HIMA, ODQ plus iberiotoxin, a selective blocker of large-conductance Ca<sup>2+</sup>-activated K<sup>+</sup> (BKCa) channels, produced greater inhibition than ODQ alone. We showed that the cGMP pathway plays a significant role in the vasorelaxant effect of nicorandil on HSV and HIMA. It seems that nicorandil directly opens KATP channels in both vessels and BKCa channels in HIMA, although it is possible that stimulation of GC contributes to KATP channels activation in HIMA. Contrary, the activation of KV channels in HSV is probably due to GC activation and increased levels of cGMP.

Martini, R. P., & Larson, D. M. (2015). Clinical evaluation and airway management for adults with cervical spine instability. *Anesthesiology Clinics*,

Airway management of patients with cervical spine instability may be difficult as a result of immobilization, and may be associated with secondary neurologic injury related to cervical spine motion. Spinal cord instability is most common in patients with trauma, but there are additional congenital and acquired conditions that predispose to subacute cervical spine instability. Patients with suspected instability should receive immobilization during airway management with manual in-line stabilization. The best strategy for airway management is one that applies the technique with the highest likelihood of success on the first attempt and the lowest biomechanical influence on a potentially unstable spine. © 2015 Elsevier Inc.

Marusina, K., Welsch, D. J., Rose, L., Brock, D., Bahr, N., Cohen, A. M., et al. (2014). *Partnerships for drug repositioning: Lessons from the CTSA pharmaceutical assets portal* Wiley Blackwell.

Drug repositioning, or finding new uses for existing compounds, is a novel approach to drug development, with great potential for reducing the time and cost of bringing a new treatment to the market. The mission of the CTSA Pharmaceutical Assets Portal has been to facilitate collaborations between industry and academic investigators for discovery of new indications for compounds that are no longer being actively developed by pharmaceutical companies. While the ultimate goal of creating a shared repository accessible to the academic community remains to be achieved, to date, the Pharma Portal has created an infrastructure that includes a national database of principal investigators with their respective biological models and delivery systems; a foci-of-expertise collaboration tool; a facility to house and maintain a compound repository; and a funding partner for repositioning studies. In summary, the Pharma Portal has created a strategy and a mechanism to support future opportunities for public-private partnerships in drug repositioning. © 2014 by John Wiley & Sons, Inc. All rights reserved.

Marx, P., Meiers, M., & Brückner, R. (2015). Activity of the response regulator CiaR in mutants of streptococcus pneumoniae R6 altered in acetyl phosphate production. *Frontiers in Microbiology*, 6(JAN)

The two-component regulatory system (TCS) CiaRH of *Streptococcus pneumoniae* is implicated in

competence,  $\beta$ -lactam resistance, maintenance of cell integrity, bacteriocin production, host colonization, and virulence. Depending on the growth conditions, CiaR can be highly active in the absence of its cognate kinase CiaH, although phosphorylation of CiaR is required for DNA binding and gene regulation. To test the possibility that acetyl phosphate (AcP) could be the alternative phosphodonor, genes involved in pyruvate metabolism were disrupted to alter cellular levels of acetyl phosphate. Inactivating the genes of pyruvate oxidase SpxB, phosphotransacetylase Pta, and acetate kinase AckA, resulted in very low AcP levels and in strongly reduced CiaR-mediated gene expression in CiaH-deficient strains. Therefore, alternative phosphorylation of CiaR appears to proceed via AcP. The AcP effect on CiaR is not detected in strains with CiaH. Attempts to obtain elevated AcP by preventing its degradation by acetate kinase AckA, were not successful in CiaH-deficient strains with a functional SpxB, the most important enzyme for AcP production in *S. pneumoniae*. The *ciaH-spxB-ackA* mutant producing intermediate amounts of AcP could be constructed and showed a promoter activation, which was much higher than expected. Since activation was dependent on AcP, it can apparently be used more efficiently for CiaR phosphorylation in the absence of AckA. Therefore, high AcP levels in the absence of CiaH and AckA may cause extreme overexpression of the CiaR regulon leading to synthetic lethality. AckA is also involved in a regulatory response, which is mediated by CiaH. Addition of acetate to the growth medium switch CiaH from kinase to phosphatase. This switch is lost in the absence of AckA indicating metabolism of acetate is required, which starts with the production of AcP by AckA. Therefore, AckA plays a special regulatory role in the control of the CiaRH TCS. © 2015 Marx, Meiers and Brückner.

McCarthy, M. S., & Martindale, R. G. (2015). Updating your nutrition care practice: Delivering evidence-based nutritional therapy to critically ill patients. *Nursing Critical Care*, 10(1), 18-26. We reviewed some of the latest evidence surrounding nutrition care practices for nurses managing nutrition therapy for acutely ill and critically ill populations. There's much we still don't know about the benefits or harms related to EN therapy, but hope that future, high-quality, randomized controlled trials in this population assist us with closing the knowledge and practice gaps as part of the imperative for science-driven healthcare in 2020. Copyright © 2015 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

McCully, S. P., Lee, T. H., McCully, B. H., Sands, C. L., Rick, E. A., Dean, R. K., et al. (2014).

Reconstitution fluid type does not affect pulmonary inflammation or DNA damage following infusion of lyophilized plasma. *Journal of Trauma and Acute Care Surgery*, 78(2), 231-239.

Background: Dysfunctional inflammation following traumatic hemorrhage can lead to multiple-organ failure and death. In our polytrauma swine model, lyophilized plasma (LP) reconstituted with sterile water and ascorbic acid suppressed systemic inflammation and attenuated DNA

damage. However, it remains unknown whether the inflammatory response is affected by the

type of fluid used to reconstitute LP. We hypothesized that common resuscitation fluids such as normal saline (LP-NS), lactated Ringer's solution (LP-LR), Hextend (LP-HX), or sterile water (LP-

SW) would yield similar inflammation profiles and DNA damage following LP reconstitution and

transfusion. Methods: This was a randomized, prospective, blinded animal study. LP was

reconstituted to 50% of original volume with NS, LR, HX, or SW buffered with 15-mM ascorbic

acid. Forty swine were subjected to a validated model of polytrauma, hemorrhagic shock, and

Grade V liver injury and resuscitated with LP. Serum interleukin 6 (IL-6), IL-10, plasma C-

reactive protein, and 8-hydroxy-2-deoxyguanosine concentrations were assessed for systemic

inflammation and DNA damage at baseline, 2 hours, and 4 hours following liver injury. Lung

inflammation was evaluated by Real Time Polymerize Chain Reaction (RT-PCR). Results:

Reconstituted LP pH was similar between groups before resuscitation. IL-6 and IL-10 increased at

2 hours and 4 hours compared with baseline in all groups ( $p < 0.017$ ). DNA damage increased at

2 hours and 4 hours compared with baseline and from 2 hours to 4 hours in the LP-NS, LP-LR,

and LP-SW groups (all  $p < 0.017$ ). Animals resuscitated with LP-HX not only demonstrated

increased DNA damage at 4 hours versus baseline but also had the lowest C-reactive protein

level at 2 hours and 4-hours ( $p < 0.017$ ). Overall, differences between groups were similar for

DNA damage and lung inflammation. Conclusion: Reconstitution fluid type does not affect

inflammatory cytokine profiles or DNA damage following LP transfusion in this swine polytrauma

model. Based on universal availability, these data suggest that sterile water is the most logical

choice for LP reconstitution in humans. Copyright © 2015 by Wolters Kluwer Health, Inc. All

rights reserved.

McDonagh, M. S., Blazina, I., Dana, T., Cantor, A., & Bougatsos, C. (2015). Screening and routine supplementation for iron deficiency anemia: A systematic review. *Pediatrics*, *135*(4), 723-733.

BACKGROUND AND OBJECTIVES: Supplementation and screening for iron-deficiency anemia (IDA) in young children may improve growth and development outcomes. The goal of this study was to review the evidence regarding the benefits and harms of screening and routine supplementation for IDA for the US Preventive Services Task Force. METHODS: We searched Medline and Cochrane databases (1996-August 2014), as well as reference lists of relevant systematic reviews. We included trials and controlled observational studies regarding the effectiveness and harms of routine iron supplementation and screening in children ages 6 to 24 months conducted in developed countries. One author extracted data, which were checked for accuracy by a second author. Dual quality assessment was performed. RESULTS: No studies of iron supplementation in young children reported on the diagnosis of neurodevelopmental delay. Five of 6 trials sparsely reporting various growth outcomes found no clear benefit of supplementation. After 3 to 12 months, Bayley Scales of Infant Development scores were not significantly different in 2 trials. Ten trials assessing iron supplementation in children reported inconsistent findings for hematologic measures. Evidence regarding the harms of supplementation was limited but did not indicate significant differences. No studies assessed the benefits or harms of screening or the association between improvement in impaired iron status and clinical outcomes. Studies may have been underpowered, and control factors varied and could have confounded results. CONCLUSIONS: Although some evidence on supplementation for IDA in young children indicates improvements in hematologic values, evidence on clinical outcomes is lacking. No randomized controlled screening studies are available.

McFarland, T. J., Rhoads, A. D., Hartzell, M., Emerson, G. G., Bhavsar, A. R., & Stout, J. T. (2015). Bevacizumab levels in breast milk after long-term intravitreal injections. *Retina (Philadelphia, Pa.)*,

PURPOSE: The purpose of this study is to determine whether bevacizumab is detectable in the breast milk of nursing mothers. METHODS: Breast milk samples were collected from 2 patients receiving monthly intravitreal bevacizumab injections for choroidal neovascularization over the course of 16 months. Enzyme-linked immunosorbent assay and Western blot analysis was used

to determine the levels of bevacizumab in the milk samples. RESULTS: An enzyme-linked immunosorbent assay was developed using antibodies specific to bevacizumab in which the sensitivity threshold was 3 ng/mL. All breast milk samples assayed from the two patients actively undergoing treatment did not have detectable levels of bevacizumab. Samples collected 1.5 hours and 7 hours after an injection and 2 randomly chosen samples were negative by Western blot analysis. CONCLUSION: A sensitive assay to detect bevacizumab in breast milk samples assayed suggests that intravitreal injections do not result in detectable bevacizumab in breast milk.

Meeker, A. S., Herink, M. C., Haxby, D. G., & Hartung, D. M. (2015). The safety and efficacy of vortioxetine for acute treatment of major depressive disorder: A systematic review and meta-analysis. *Systematic Reviews*, 4(1), 21-015-0001-y.

BACKGROUND: Vortioxetine is the first mixed serotonin agonist and antagonist antidepressant approved in the US. We sought to evaluate all published and unpublished data available to determine the efficacy and harms of vortioxetine in adults with major depressive disorder.

METHODS: We used a predefined search strategy of MEDLINE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and Drugs@FDA to identify studies evaluating vortioxetine in the acute treatment of major depressive disorder. Only randomized controlled trials (RCTs) that provided results on relevant clinical efficacy and safety outcomes were included. Study quality was assessed and results were pooled using mixed effect meta-analyses where applicable.

RESULTS: We identified 11 RCTs with 6,145 participants meeting inclusion criteria (eight were published and three were unpublished). The trials did not exceed 8 weeks in duration. The response rate with vortioxetine was significantly higher for 1-mg (relative risk (RR) = 1.91; 95% confidence interval (CI) 1.36 to 2.69), 5-mg (RR = 1.33; 95% CI 1.10 to 1.61), 10-mg (RR = 1.42; 95% CI 1.21 to 1.67), and 20-mg doses (RR = 1.58; 95% CI 1.19 to 2.08) compared to placebo. Remission rates were significantly higher for the 10-mg group (RR = 1.45; 95% CI 1.18 to 1.77) and the 20-mg group (RR = 1.68; 95% CI 1.19 to 2.37) compared to placebo. Meta-regression of dose on the log odds ratio of response was not statistically significant (beta = 0.01; P = 0.46). Vortioxetine response rates were lower than active serotonin and norepinephrine reuptake inhibitor (SNRI) comparators for the 5-mg (RR = 0.88; 95% CI 0.80 to 0.98), 15-mg

(RR = 0.78; 95% CI 0.68 to 0.90), and 20-mg (RR = 0.82; 95% CI 0.72 to 0.94) doses. The most common adverse events were nausea and vomiting which increased in frequency with higher doses. CONCLUSIONS: Vortioxetine was significantly more effective than placebo for acute treatment of major depressive disorder (MDD). Although treatment effect estimates varied substantially between studies, a dose effect was not observed. Vortioxetine does not appear to be more effective, and is potentially less effective, than an SNRI. SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42013006198 .

Mehta, P. A., Zhang, M. J., Eapen, M., He, W., Seber, A., Gibson, B., et al. (2015). Transplant outcomes for children with hypodiploid acute lymphoblastic leukemia. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*, Children with hypodiploid acute lymphoblastic leukemia (ALL) have inferior outcomes despite intensive risk adapted chemotherapy regimens. We describe 78 children with hypodiploid ALL who underwent hematopoietic stem cell transplant (HSCT) between 1990 and 2010. Thirty nine (50%) patients had  $\neq$ CR2. Twenty nine patients (37%) received a graft from a related donor and 49 (63%) from an unrelated donor. All patients received a myeloablative conditioning regimen. The 5-year probabilities of leukemia-free survival (LFS), overall survival (OS), relapse, and treatment related mortality (TRM) for the entire cohort were 51%, 56%, 27% and 22% respectively. Multivariate analysis confirmed that mortality risks were higher for patients transplanted in CR2 (HR 2.16,  $p=0.05$ ), with chromosome number  $\leq 43$  (HR 2.15,  $p=0.05$ ) and for those transplanted in the first decade of the study period (HR 2.60,  $p=0.01$ ). Similarly, treatment failure risks were higher with chromosome number  $\leq 43$  (HR 2.28,  $p=0.04$ ) and the earlier transplant period (HR 2.51,  $p=0.01$ ). Although survival is better with advances in donor selection and supportive care, disease-related risk factors significantly influence transplantation outcomes.

Mertens, A. C., Yong, J., Dietz, A. C., Kreiter, E., Yasui, Y., Bleyer, A., et al. (2015). Conditional survival in pediatric malignancies: Analysis of data from the childhood cancer survivor study and the surveillance, epidemiology, and end results program. *Cancer*, 121(7), 1108-1117. BACKGROUND Long-term survivors of pediatric cancer are at risk of life-threatening late effects

of their cancer. Previous studies have shown excesses in long-term mortality within high-risk groups defined by demographic and treatment characteristics. **METHODS** To investigate conditional survival in a pediatric cancer population, the authors performed an analysis of conditional survival in the original Childhood Cancer Survivor Study (CCSS) cohort and the Surveillance, Epidemiology, and End Results (SEER) database registry. The overall probability of death for patients at 5 years and 10 years after they survived 5, 10, 15, and 20 years since cancer diagnosis and cause-specific death in 10 years for 5-year survivors were estimated using the cumulative incidence method. **RESULTS** Among patients in the CCSS and SEER cohorts who were alive 5 years after their cancer diagnosis, within each diagnosis group at least 92% were alive in the subsequent 5 years, except for patients with leukemia, of whom only 88% of 5-year survivors remained alive in the subsequent 5 years. The probability of all-cause mortality in the next 10 years among patients who survived at least 5 years after diagnosis was 8.8% in CCSS and 10.6% in SEER, approximately 75% of which was due to neoplasms as the cause of death. **CONCLUSIONS** The risk of death among survivors of pediatric cancer in 10 years can vary between diagnosis groups by at most 12%, even up to 20 years after diagnosis. This information is clinically significant when counseling patients regarding their conditional survival, particularly when survivors are seen in long-term follow-up. *Cancer* 2015;121:1108-1117. © 2014 American Cancer Society.

Merz, C., Saller, S., Kunz, L., Xu, J., Yeoman, R. R., Ting, A. Y., et al. (2015). Expression of the beta-2 adrenergic receptor (ADRB-2) in human and monkey ovarian follicles: A marker of growing follicles? *Journal of Ovarian Research*, 8(1)

Background: ADRB-2 was implicated in rodent ovarian functions, including initial follicular growth. In contrast, ADRB-2 expression and function in nonhuman primate and human ovary were not fully known but innervation and significant levels of norepinephrine (NE), which is a ligand at the ADRB-2, were reported in the ovary. Methods: We studied expression of ADRB-2 in human and rhesus monkey ovary (RT-PCR, immunohistochemistry; laser micro dissection) and measured levels of norepinephrine (NE; ELISA) in monkey follicular fluid (FF). 3D cultures of monkey follicles (4 animals) were exposed to NE or the ADRB-2 agonist isoproterenol (ISO), and follicular development (size) was monitored. Upon termination expression of ADRB-2, FSH receptor and

aromatase genes were examined. Results: Immunohistochemistry and RT-PCR of either human follicular granulosa cells (GCs) obtained by laser micro dissection or isolated monkey follicles revealed ADRB-2 in GCs of primordial, primary, secondary and tertiary follicles. Staining of GCs in primordial and primary follicles was intense. In large preantral and antral follicles the staining was heterogeneous, with positive and negative GCs present but GCs lining the antrum of large follicles were generally strongly immunopositive. Theca, interstitial, and ovarian surface epithelial cells were also positive. NE was detected in FF of preovulatory antral monkey follicles ( $0.37 \pm 0.05$  ng/ml;  $n=7$ ; ELISA) but not in serum. We examined preantral follicles ranging from 152 to 366  $\mu$ m in diameter in a 3D culture in media supplemented with follicle stimulating hormone (FSH). Under these conditions, neither NE, nor ISO, influenced growth rate in a period lasting up to one month. Upon termination of the cultures, all surviving follicles expressed aromatase and FSH receptors, but only about half of them also co-expressed ADRB-2. The ADRB-2 expression was not correlated with the treatment but was positively correlated with the follicular size at the beginning and at the end of the culture period. Hence, expression of ADRB-2 was found in the largest and fastest-in vitro growing follicles. Conclusions: The results imply ADRB-2-mediated actions in the development of primate follicles. Drugs interfering with ADRB-2 are used to treat medical conditions and may have unexplored effects in the human ovary. © 2015 Merz et al.; licensee BioMed Central.

Metcalf, T. U., Cubas, R. A., Ghneim, K., Cartwright, M. J., Grevenynghe, J. V., Richner, J. M., et al. (2015). Global analyses revealed age-related alterations in innate immune responses after stimulation of pathogen recognition receptors. *Aging Cell*, *14*(3), 421-432.

Aging leads to dysregulation of multiple components of the immune system that results in increased susceptibility to infections and poor response to vaccines in the aging population. The dysfunctions of adaptive B and T cells are well documented, but the effect of aging on innate immunity remains incompletely understood. Using a heterogeneous population of peripheral blood mononuclear cells (PBMCs), we first undertook transcriptional profiling and found that PBMCs isolated from old individuals ( $\geq 65$  years) exhibited a delayed and altered response to stimulation with TLR4, TLR7/8, and RIG-I agonists compared to cells obtained from adults ( $\leq 40$  years). This delayed response to innate immune agonists resulted in the reduced production of

pro-inflammatory and antiviral cytokines and chemokines including TNF $\alpha$ , IL-6, IL-1 $\beta$ , IFN $\alpha$ , IFN $\gamma$ , CCL2, and CCL7. While the major monocyte and dendritic cell subsets did not change numerically with aging, activation of specific cell types was altered. PBMCs from old subjects also had a lower frequency of CD40+ monocytes, impaired up-regulation of PD-L1 on monocytes and T cells, and increased expression of PD-L2 and B7-H4 on B cells. The defective immune response to innate agonists adversely affected adaptive immunity as TLR-stimulated PBMCs (minus CD3 T cells) from old subjects elicited significantly lower levels of adult T-cell proliferation than those from adult subjects in an allogeneic mixed lymphocyte reaction (MLR). Collectively, these age-associated changes in cytokine, chemokine and interferon production, as well as co-stimulatory protein expression could contribute to the blunted memory B- and T-cell immune responses to vaccines and infections. © 2015 The Authors.

Meyer, C., Walker, J., Dewane, J., Engelmann, F., Laub, W., Pillai, S., et al. (2015). Impact of irradiation and immunosuppressive agents on immune system homeostasis in rhesus macaques. *Clinical and Experimental Immunology*,

In this study we examined the effects of non-myeloablative total body irradiation (TBI) in combination with immunosuppressive chemotherapy on immune homeostasis in rhesus macaques. Our results show administration of cyclosporine A or tacrolimus without radiotherapy did not result in lymphopenia. The addition of TBI to the regimen resulted in lymphopenia as well as alterations in the memory/naive ratio following reconstitution of lymphocyte populations. Dendritic cell (DC) numbers in whole blood were largely unaffected while the monocyte population was altered by immunosuppressive treatment. Irradiation also resulted in increased levels of circulating cytokines and chemokines that correlated with T cell proliferative bursts and with the shift toward memory T cells. We also report that Anti-thymocyte globulin (ATG) treatment and CD3 immunotoxin administration resulted in a selective and rapid depletion of naive CD4 and CD8 T cells and increased frequency of memory T cells. We also examined the impact of these treatments on reactivation of latent simian varicella virus (SVV) infection as a model of varicella zoster virus (VZV) infection of humans. None of the treatments resulted in overt SVV reactivation; however, select animals had transient increases in SVV-specific T cell responses following immunosuppression suggestive of subclinical reactivation. Overall, we

provide detailed observations into immune modulation by TBI and chemotherapeutic agents in rhesus macaques, an important research model of human disease. This article is protected by copyright. All rights reserved.

Midgett, M., & Rugonyi, S. (2015). Analysis of 4D myocardial wall motion during early stages of chick heart development. *Methods in Molecular Biology (Clifton, N.J.)*, 1299, 191-212.

4D myocardial wall motion analysis (3D structure over time) during early embryonic stages of chick heart development provides a comprehensive view to characterize the biomechanical environment of cardiac growth. Myocardial wall strains, velocity, and area shortening over the cardiac cycle are common wall motion assessments and can be accurately measured from 4D datasets. Here, we describe how to employ a variety of image modalities (optical, ultrasound, and optical coherence tomography imaging) and analysis techniques to extract quantitative measures of myocardial wall motion.

Mitin, T., Enestvedt, C. K., & Thomas, C. R., Jr. (2015). Management of oligometastatic rectal cancer: Is liver first? *Journal of Gastrointestinal Oncology*, 6(2), 201-207.

Twenty percent of patients with rectal cancer present with synchronous liver metastases at the time of initial diagnosis. These patients can be treated with a curative intent, although the choice and sequence of treatment modalities are not well established and are commonly debated in multi-disciplinary tumor boards. In this article we review clinical evidence for various treatment approaches and attempt to formulate a pathway for clinicians to use in evaluating and managing these patients.

Mitin, T., Hunter, J. G., & Thomas, C. R., Jr. (2015). To the editor. *New England Journal of Medicine*, 372(15), 1471-1472.

Mo, D., Fleseriu, M., Qi, R., Jia, N., Child, C. J., Bouillon, R., et al. (2015). Fracture risk in adult patients treated with growth hormone replacement therapy for growth hormone deficiency: A prospective observational cohort study. *The Lancet. Diabetes & Endocrinology*,  
BACKGROUND: To our knowledge, no controlled studies of the effects of long-term growth hormone replacement on fracture risk in adult patients with growth hormone deficiency exist. We

assessed the effect of growth hormone treatment on fracture risk in patients with growth hormone deficiency from the international Hypopituitary Control and Complications Study (HypoCCS) surveillance database. METHODS: In this prospective cohort study, patients with growth hormone deficiency were analysed from the HypoCCS database of adults with hypopituitarism from the USA, Canada, Japan, and 14 European countries. Patients were eligible if they were aged 18 years or older and had an established diagnosis of growth hormone deficiency, either alone or with multiple pituitary hormone deficiencies, as identified by clinical history and biochemical testing. Patients were assessed over a mean follow-up period of 4.6 years (SD 3.8). The effect of growth hormone treatment on fracture risk was assessed by Cox proportional hazard modelling with adjustment for several confounders. FINDINGS: Between Jan 3, 1996, and Dec 15, 2012, we enrolled 10 673 patients to this study. Of the enrolled patients, 1032 patients were excluded from assessment because of incomplete data, leaving 9641 in the analysis cohort. Of these patients, 8374 of received growth hormone and 1267 did not. Annual fracture incidence rate was lower in patients who received growth hormone than in those who did not (fracture incidence rate 1.19% vs 1.91%, hazard ratio [HR] 0.69, 95% CI 0.54-0.88). However, no difference in fracture risk was observed between patients who did and did not receive growth hormone treatment in the subgroup of patients with pre-existing osteoporosis (n=826; 0.97, 0.48-1.95). INTERPRETATION: Our results suggest that growth hormone replacement therapy could be protective against fracture for adult patients with growth hormone deficiency without previously reported osteoporosis. Starting growth hormone therapy before the onset of osteoporosis might be optimum for bone health of adult patients with growth hormone deficiency. FUNDING: Eli Lilly and Co.

Molfenter, T., Sherbeck, C., Zehner, M., Quanbeck, A., McCarty, D., Kim, J. S., et al. (2015).

Implementing buprenorphine in addiction treatment: Payer and provider perspectives in ohio. *Substance Abuse Treatment, Prevention, and Policy*, 10(1), 13.

BACKGROUND: Buprenorphine is under-utilized in treating opioid addiction. Payers and providers both have substantial influence over the adoption and use of this medication to enhance recovery. Their views could provide insights into the barriers and facilitators in buprenorphine adoption. METHODS: We conducted individual interviews with 18 Ohio county Alcohol, Drug

Addiction, and Mental Health Services (ADAMHS) Boards (payers) and 36 addiction treatment centers (providers) to examine barriers and facilitators to buprenorphine use. Transcripts were reviewed, coded, and qualitatively analyzed. First, we examined reasons that county boards supported buprenorphine use. A second analysis compared county boards and addiction treatment providers on perceived barriers and facilitators to buprenorphine use. The final analysis compared county boards with low and high use of buprenorphine to determine how facilitators and barriers differed between those settings. RESULTS: County boards (payers) promoted buprenorphine use to improve clinical care, reduce opioid overdose deaths, and prepare providers for participation in integrated models of health care delivery with primary care clinics and hospitals. Providers and payers shared many of the same perceptions of facilitators and barriers to buprenorphine use. Common facilitators identified were knowledge of buprenorphine benefits, funds allocated to purchase buprenorphine, and support from the criminal justice system. Common barriers were negative attitudes toward use of agonist pharmacotherapy, payment environment, and physician prescribing capacity. County boards with low buprenorphine use rates cited negative attitudes toward use of agonist medication as a primary barrier. County boards with high rates of buprenorphine use dedicated funds to purchase buprenorphine in spite of concerns about limited physician prescribing capacity. CONCLUSIONS: This qualitative analysis found that attitudes toward use of medication and medication funding environment play important roles in an organization's decision to begin buprenorphine use and that physician availability influences an organization's ability to expand buprenorphine use over time. Additional education, reimbursement support, and policy changes are needed to support buprenorphine adoption and use, along with a greater understanding of the roles payers, providers, and regulators play in the adoption of targeted practices.

Molis, M. R., Kappel, S. D., McMillan, G. P., Gallun, F. J., Dann, S. M., & Konrad-Martin, D. (2015). Effects of hearing and aging on sentence-level time-gated word recognition. *Journal of Speech, Language, and Hearing Research, 58*(2), 481-496.

Purpose: Aging is known to influence temporal processing, but its relationship to speech perception has not been clearly defined. To examine listeners' use of contextual and phonetic information, the Revised Speech Perception in Noise test (R-SPIN) was used to develop a time-

gated word (TGW) task. Method: In Experiment 1, R-SPIN sentence lists were matched on context, target-word length, and median word segment length necessary for target recognition. In Experiment 2, TGW recognition was assessed in quiet and in noise among adults of various ages with normal hearing to moderate hearing loss. Linear regression models of the minimum word duration necessary for correct identification and identification failure rates were developed. Age and hearing thresholds were modeled as continuous predictors with corrections for correlations among multiple measurements of the same participants. Results: While aging and hearing loss both had significant impacts on task performance in the most adverse listening condition (low context, in noise), for most conditions, performance was limited primarily by hearing loss. Conclusion: Whereas hearing loss was strongly related to target-word recognition, the effect of aging was only weakly related to task performance. These results have implications for the design and evaluation of studies of hearing and aging. © 2015 American Speech-Language-Hearing Association

Moneta, G. (2006). *Conventional carotid doppler ultrasound* Cambridge University Press.

This chapter provides an overview of the traditional and evolving criteria used for grading carotid artery stenosis as well as the clinical relevance of sonography in the management of symptomatic and asymptomatic carotid disease. Additionally, discussions of carotid restenosis after endarterectomy as well as the diagnostic difficulties imposed by internal carotid coils and kinks, bilateral highgrade carotid stenosis and carotid stenting are included. Technical points Brachial systolic and diastolic blood pressures are measured in each arm. The carotid duplex ultrasound examination includes the carotid and vertebral arteries bilaterally, as stipulated by vascular laboratory accrediting organizations. Because the flow characteristics in one carotid artery may be influenced significantly by the status of the contralateral carotid artery, it is important to perform bilateral carotid examinations. A very high-grade stenosis or occlusion of one common or internal carotid artery can result in increased compensatory flow in the opposite vessel (Fujitani et al., 1992). The velocity readings in the patent artery therefore are higher than expected and may suggest a greater degree of stenosis than is actually present. The ultrasound examination should include both longitudinal and transverse views of the vessels. Vessel diameter measurements, visual assessment of stenosis severity, and plaque assessments should be done

in the transverse plane. Doppler waveforms should be generated from the longitudinal plane.

Gray-scale images alert the examiner to the presence of plaque in the arterial wall, while changes in the hue of the color flow pattern suggest the presence of stenosis. © Cambridge University Press 2007 and 2009.

Morgans, C. W. (2015). All ON pathways are not alike. *The Journal of Physiology*, 593(7), 1527-1528.

Morris, C. J., Yang, J. N., Garcia, J. I., Myers, S., Bozzi, I., Wang, W., et al. (2015). Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 112(17), E2225-34.

Glucose tolerance is lower in the evening and at night than in the morning. However, the relative contribution of the circadian system vs. the behavioral cycle (including the sleep/wake and fasting/feeding cycles) is unclear. Furthermore, although shift work is a diabetes risk factor, the separate impact on glucose tolerance of the behavioral cycle, circadian phase, and circadian disruption (i.e., misalignment between the central circadian pacemaker and the behavioral cycle) has not been systematically studied. Here we show-by using two 8-d laboratory protocols-in healthy adults that the circadian system and circadian misalignment have distinct influences on glucose tolerance, both separate from the behavioral cycle. First, postprandial glucose was 17% higher (i.e., lower glucose tolerance) in the biological evening (8:00 PM) than morning (8:00 AM; i.e., a circadian phase effect), independent of the behavioral cycle effect. Second, circadian misalignment itself (12-h behavioral cycle inversion) increased postprandial glucose by 6%. Third, these variations in glucose tolerance appeared to be explained, at least in part, by different mechanisms: during the biological evening by decreased pancreatic beta-cell function (27% lower early-phase insulin) and during circadian misalignment presumably by decreased insulin sensitivity (elevated postprandial glucose despite 14% higher late-phase insulin) without change in early-phase insulin. We explored possible contributing factors, including changes in polysomnographic sleep and 24-h hormonal profiles. We demonstrate that the circadian system importantly contributes to the reduced glucose tolerance observed in the evening compared with

the morning. Separately, circadian misalignment reduces glucose tolerance, providing a mechanism to help explain the increased diabetes risk in shift workers.

Muldoon, L. L., Wu, Y. J., Pagel, M. A., & Neuwelt, E. A. (2015). N-acetylcysteine chemoprotection without decreased cisplatin antitumor efficacy in pediatric tumor models. *Journal of Neuro-Oncology*, *121*(3), 433-440.

Decreasing oxidative damage with the antioxidant agent N-acetylcysteine (NAC) can block the side effects of chemotherapy, but may diminish anti-tumor efficacy. We tested the potential for interactions of high dose NAC against a minimally effective cisplatin chemotherapy regimen in rat models of human pediatric cancers. Athymic rats received subcutaneous implantation of human SK-N-AS neuroblastoma cells or intra-cerebellar implantation of human D283-MED medulloblastoma cells. Rats were untreated or treated with cisplatin (3 or 4 mg/kg IV) with or without NAC (1,000 mg/kg IV) 30 min before or 4 h after cisplatin treatment. Blood urea nitrogen (BUN) and tumor volumes were measured. Cisplatin decreased the growth of SK-N-AS neuroblastoma subcutaneous tumors from  $17.7 \pm 4.9$  to  $6.4 \pm 2.5$  fold over baseline 2 weeks after treatment ( $P < 0.001$ ). Pretreatment with NAC decreased cisplatin efficacy, while 4 h delayed NAC did not significantly affect cisplatin anti-tumor effects (relative tumor volume  $6.8 \pm 2.0$  fold baseline,  $P < 0.001$ ). In D283-MED medulloblastoma brain tumors, cisplatin decreased final tumor volume to  $3.9 \pm 2.3$  mm<sup>3</sup> compared to untreated tumor volume of  $45.9 \pm 38.7$  ( $P = 0.008$ ). Delayed NAC did not significantly alter cisplatin efficacy (tumor volume  $6.8 \pm 8.1$  mm<sup>3</sup>,  $P = 0.014$  versus control). Cisplatin was minimally nephrotoxic in these models. NAC decreased cisplatin-induced elevations in BUN ( $P < 0.02$ ). NAC chemoprotection did not alter cisplatin therapy, if delayed until 4 h after chemotherapy. These data support a Phase I/II clinical trial of delayed NAC to reduce ototoxicity in children with localized pediatric cancers. © 2014, International Organization for Biological Control (outside the USA).

Müller, T. D., Nogueiras, R., Andermann, M. L., Andrews, Z. B., Anker, S. D., Argente, J., et al. (2015). Ghrelin. *Molecular Metabolism*,

Background: The gastrointestinal peptide hormone ghrelin was discovered in 1999 as the endogenous ligand of the growth hormone secretagogue receptor. Increasing evidence supports

more complicated and nuanced roles for the hormone, which go beyond the regulation of systemic energy metabolism. Scope of review: In this review, we discuss the diverse biological functions of ghrelin, the regulation of its secretion, and address questions that still remain 15 years after its discovery. Major conclusions: In recent years, ghrelin has been found to have a plethora of central and peripheral actions in distinct areas including learning and memory, gut motility and gastric acid secretion, sleep/wake rhythm, reward seeking behavior, taste sensation and glucose metabolism. © 2015 The Authors.

Murray, J. F., & Buist, A. S. (2015). *Respiratory disorders related to smoking tobacco* S. Karger AG.

Respiratory disorders are among the most frequent causes of death and severe disability from the steadily worsening global pandemic of smoking tobacco. Two disorders stand out: lung cancer and chronic obstructive pulmonary disease (COPD). First, lung cancer caused 1.59 million deaths worldwide in 2012, more than the next two top cancer causes combined (liver and stomach). Tobacco smoke induces pathologic changes in the bronchial epithelium that often progress to fatal invasive lung cancer. For the first time, the recent US National Lung Screening Trial reported a significant (20%) reduction in lung cancer mortality in current or previous heavy smokers detected by low-dose, spiral computed tomography. Second, dramatic advances in understanding COPD include the recognition that it is a complex, multisystem disease that involves many organs-not just the lungs. COPD results from an inflammatory process leading to narrowing and scarring of small airways and destruction of lung parenchyma causing emphysema. Tobacco smoke remains the most important risk factor for COPD globally, but occupational and environmental exposures play increasing roles. Tobacco smoke is also the principal cause of certain interstitial lung diseases and worsens others. Both prenatal and postnatal tobacco exposure contribute to impairment in lung growth and development, and increase the risk of acquiring infectious pneumonias and tuberculosis. © 2015 S. Karger AG, Basel.

Nagel, B. J., & Kroenke, C. D. (2008). The use of magnetic resonance spectroscopy and magnetic resonance imaging in alcohol research. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(3), 243-246.

The recent emergence of magnetic resonance (MR)-based neuroimaging techniques has

dramatically improved researchers' ability to understand the neuropathology of alcoholism. These techniques range from those that directly monitor the metabolism and the biochemical and physiological effects (i.e., the pharmacodynamics) of alcohol within the brain to techniques that examine the impact of heavy alcohol use on brain structure and function. In general, MR-based techniques measure electromagnetic signals (the same type of signals detected by a radio antenna) generated by nuclei of endogenous molecules in the body of a person placed in a powerful magnet field. When influenced by a magnet, tissue itself transiently becomes magnetic. In part, this is because of the properties of atomic nuclei. Different MR-based techniques have been developed to utilize nuclear magnetism induced in tissue to generate images of internal structure. The most commonly used MR imaging (MRI) techniques rely on signals derived from hydrogen nuclei in water, which is by far the most concentrated molecular species in the body. The physical properties of water molecules vary from one region of tissue to another, and this influences the nuclear magnetism generated by water hydrogen nuclei. As a result, MRI can differentiate regions in soft tissue at a high level of detail. A second approach-MR spectroscopy (MRS)- uses the same strategy to detect electromagnetic signals, but they are derived from nuclei of atoms (hydrogen as well as some other atoms) on molecules other than water, such as lipids, amino acids, or even alcohol (i.e., ethanol). The resulting data on the molecule(s) under investigation can provide detailed information about the metabolic activity of various tissues, including the brain. The main advantage of MR-based techniques is that they do not expose the subject to radioactive tracers and therefore can be used repeatedly in the same subject, allowing researchers to track metabolic or structural changes over time. This article briefly summarizes how these techniques may be used to characterize the effects of alcohol dependence on the brain.

Najjar, R. H., Lyman, B., & Miehl, N. (2015). Nursing students' experiences with high-fidelity simulation. *International Journal of Nursing Education Scholarship*, 12(1), 1-9.

Research has revealed the effectiveness of simulation for facilitating student development of self-efficacy, knowledge, clinical judgment, and proficiency in technical skills. This grounded theory study was conducted to describe the experience of nursing students in high-fidelity simulation and develop a model which explicates the experience of nursing students in simulation. Focus

group interviews were conducted with three cohorts of students enrolled in a baccalaureate nursing program who experienced simulation four to twelve times per academic year. Five prominent themes emerged during analysis Emotional Processing; Anxiety; Making Connections; Fidelity; and Learning. The Simulation Learning Model - Student Experience (SLM-SE) was developed to illustrate the student's multi-dimensional experience of learning through high-fidelity simulation. Findings from this study suggest that students are better equipped to learn through increasing confidence and experience, continued reflection-on action and enhanced peer-to-peer interaction. Recommendations for future research include developing strategies to optimize students' experiences for learning in simulation. © 2015 by De Gruyter.

Naugler, W. E., Alsina, A. E., Frenette, C. T., Rossaro, L., & Sellers, M. T. (2015). Building the multidisciplinary team for management of patients with hepatocellular carcinoma. *Clinical Gastroenterology and Hepatology*, 13(5), 827-835.

Optimal care of the patient with hepatocellular carcinoma (HCC) necessitates the involvement of multiple providers. Because the patient with HCC often carries 2 conditions with competing mortality risks (cancer and underlying cirrhosis), no single provider is equipped to deal with all of these patients' needs adequately. Multidisciplinary teams (MDTs) have evolved to facilitate care coordination, reassessments of clinical course, and nimble changes in treatment plans required for this complex group of patients. Providers or sites that elect to manage patients with HCC thus are increasingly aware of the need to build their own MDT or communicate with an established one. The availability of new communication technologies, such as teleconferencing or teleconsultation, offers the possibility of MDT expansion into underserved or rural areas, as well as areas such as correctional facilities. Although the availability of resources for HCC patient care varies from site to site, construction of an MDT is possible in a wide spectrum of clinical practices, and this article suggests a blueprint for assembly of such collaboration. Research strategies are needed to explain how MDTs improve clinical outcomes so that MDTs themselves can be improved. © 2015 AGA Institute.

Naval, N. S., Nyquist, P. A., & Carhuapoma, J. R. (2009). *Medical management of intracerebral hemorrhage* Cambridge University Press.

Spontaneous intracerebral hemorrhage (ICH) causes 10–15% of first ever strokes and is associated with the highest mortality of all cerebrovascular events, with 30-day mortality after ICH approaching almost 50%. Of note, most survivors never regain functional independence, with only 20% achieving a meaningful level of functional recovery at six months [1,2]. This article discusses the basic principles of management of ICH, including initial stabilization, the prevention of hematoma growth, hemodynamic goal-setting, treatment of potential complications such as cerebral edema, herniation and seizures, and identification of the underlying etiology. Newer treatment options such as minimally invasive surgery (MIS) to reduce clot size are also briefly discussed. Initial medical stabilization As in other medical emergencies, initial resuscitative measures should be directed to establishing adequacy of airway, breathing, and circulation (ABCs). Airway: indications for endotracheal intubation include the lack of adequate airway protection (Glasgow Coma Scale [GCS] Score 8 in the absence of a good cough/gag reflex who may be high aspiration risk especially with brainstem hemorrhages. Breathing: hyperventilation might be necessary in the event of acute herniation, but, extrapolating from brain trauma literature, its prophylactic use is unlikely to be of benefit. Due to the risk of cerebral ischemia with prolonged hyperventilation, cautious slow return to goals of normocarbica (PaCO<sub>2</sub> 35–45) after reversal of herniation is recommended. © J. R. Carhuapoma, S. A. Mayer, and D. F. Hanley 2010.

Neugebauer, J. M., Kwon, S., Kim, H. S., Donley, N., Tilak, A., Sopory, S., et al. (2015). The prodomain of BMP4 is necessary and sufficient to generate stable BMP4/7 heterodimers with enhanced bioactivity in vivo. *Proceedings of the National Academy of Sciences of the United States of America*,  
Bone morphogenetic proteins 4 and 7 (BMP4 and BMP7) are morphogens that signal as either homodimers or heterodimers to regulate embryonic development and adult homeostasis. BMP4/7 heterodimers exhibit markedly higher signaling activity than either homodimer, but the mechanism underlying the enhanced activity is unknown. BMPs are synthesized as inactive precursors that dimerize and are then cleaved to generate both the bioactive ligand and prodomain fragments, which lack signaling activity. Our study reveals a previously unknown requirement for the BMP4 prodomain in promoting heterodimer activity. We show that BMP4 and

BMP7 precursor proteins preferentially or exclusively form heterodimers when coexpressed in vivo. In addition, we show that the BMP4 prodomain is both necessary and sufficient for generation of stable heterodimeric ligands with enhanced activity and can enable homodimers to signal in a context in which they normally lack activity. Our results suggest that intrinsic properties of the BMP4 prodomain contribute to the relative bioactivities of homodimers versus heterodimers in vivo. These findings have clinical implications for the use of BMPs as regenerative agents for the treatment of bone injury and disease.

Newgard, C. D., Meier, E. N., McKnight, B., Drennan, I. R., Richardson, D., Brasel, K., et al. (2014).

Understanding traumatic shock: Out-of-hospital hypotension with and without other physiologic compromise. *Journal of Trauma and Acute Care Surgery*, 78(2), 342-351.

Background: Among trauma patients with out-of-hospital hypotension, we evaluated the predictive value of systolic blood pressure (SBP) with and without other physiologic compromise for identifying trauma patients requiring early critical resources. Methods: This was a secondary analysis of a prospective cohort of injured patients 13 years or older with out-of-hospital hypotension (SBP  $\leq$  90 mmHg) who were transported by 114 emergency medical service agencies to 56 Level I and II trauma centers in 11 regions of the United States and Canada from January 1, 2010, through June 30, 2011. The primary outcome was early critical resource use, defined as blood transfusion of 6 U or greater, major nonorthopedic surgery, interventional radiology, or death within 24 hours. Results: of 3,337 injured patients with out-of-hospital hypotension, 1,094 (33%) required early critical resources and 1,334 (40%) had serious injury (Injury Severity Score [ISS]  $\geq$  16). Patients with isolated hypotension required less early critical resources (14% vs. 52%), had less serious injury (20% vs. 61%), and had lower mortality (24 hours, 1% vs. 26%; in-hospital, 3% vs. 34%). The standardized probability of requiring early critical resources was lowest among patients with blunt injury and isolated moderate hypotension (0.12; 95% confidence interval, 0.09-0.15) and steadily increased with additional physiologic compromise, more severe hypotension, and penetrating injury (0.94; 95% confidence interval, 0.90-0.98). Conclusion: A minority of trauma patients with isolated out-of-hospital hypotension require early critical resuscitation resources. However, hypotension accompanied by additional physiologic compromise or penetrating injury markedly increases the probability of requiring time-sensitive

interventions. Level of Evidence: Prognostic study, level II. Copyright © 2015 by Wolters Kluwer Health, Inc. All rights reserved.

Nezhat, F. R., Apostol, R., Nezhat, C., & Pejovic, T. (2015). New insights in the pathophysiology of ovarian cancer and implications for screening and prevention. *American Journal of Obstetrics and Gynecology*,

Despite advances in medicine, ovarian cancer remains the deadliest of the gynecological malignancies. Herein we present the latest information on the pathophysiology of ovarian cancer and its significance for ovarian cancer screening and prevention. A new paradigm for ovarian cancer pathogenesis presupposes 2 distinct types of ovarian epithelial carcinoma with distinct molecular profiles: type I and type II carcinomas. Type I tumors include endometrioid, clear-cell carcinoma, and low-grade serous carcinoma and mostly arise via defined sequence either from endometriosis or from borderline serous tumors, mostly presenting in an early stage. More frequent type II carcinomas are usually high-grade serous tumors, and recent evidence suggests that the majority arise from the fimbriated end of the fallopian tube. Subsequently, high-grade serous carcinomas usually present at advanced stages, likely as a consequence of the rapid peritoneal seeding from the open ends of the fallopian tubes. On the other hand, careful clinical evaluation should be performed along with risk stratification and targeted treatment of women with premalignant conditions leading to type I cancers, most notably endometriosis and endometriomas. Although the chance of malignant transformation is low, an understanding of this link offers a possibility of prevention and early intervention. This new evidence explains difficulties in ovarian cancer screening and helps in forming new recommendations for ovarian cancer risk evaluation and prophylactic treatments.

Nguyen-Truong, C. K. Y., Leo, M. C., Lee-Lin, F., Gedaly-Duff, V., Nail, L. M., Gregg, J., et al. (2015).

Adaptation and testing of instruments to measure cervical cancer screening factors among vietnamese immigrant women. *Journal of Transcultural Nursing*, 26(3), 244-253.

Purpose: Vietnamese American women diagnosed with cervical cancer are more likely to have advanced cancer than non-Hispanic White women. We sought to (a) develop a culturally sensitive Vietnamese translation of the Revised Susceptibility, Benefits, and Barriers Scale; Cultural

Barriers to Screening Inventory; Confidentiality Issues Scale; and Quality of Care from the Health Care System Scale and (b) examine the psychometric properties. Design: Cross-sectional study with 201 Vietnamese immigrant women from the Portland, Oregon, metropolitan area. Method: We used a community-based participatory research approach and the U.S. Census Bureau's team approach to translation. Results: Cronbach's alpha ranged from .57 to .91. The incremental fit index ranged from .83 to .88. Discussion and Conclusions: The instruments demonstrated moderate to strong subscale internal consistency. Further research to assess structural validity is needed. Implications for Practice: Our approaches to translation and psychometric examination support use of the instruments in Vietnamese immigrant women. © The Author(s) 2014

Nicolaidis, C., Raymaker, D. M., Ashkenazy, E., McDonald, K. E., Dern, S., Baggs, A. E., et al. (2015).

"Respect the way I need to communicate with you": Healthcare experiences of adults on the autism spectrum. *Autism : The International Journal of Research and Practice*,

Our objective was to obtain an in-depth understanding of autistic adults' experiences with healthcare and their recommendations for improving care. Our academic-community partnership used a community-based participatory research approach to conduct semi-structured, open-ended interviews with 39 autistic adults and 16 people who had experience supporting autistic adults in healthcare settings. Participants identified patient-level, autism-related factors that impact healthcare interactions, including verbal communication skills, sensory sensitivities, challenges with body awareness, slow processing speed, atypical non-verbal communication, and challenges with organization. However, the success of healthcare interactions largely depended on the interplay between patient- and provider-level factors, as well as the larger context in which patients were receiving care. Provider-level factors included providers' knowledge about autism in adults, incorrect assumptions about individual patients, willingness to allow written communication, use of accessible language, openness to providing other accommodations, and skill in appropriately incorporating supporters. System-level factors included the availability of supporters, complexity of the healthcare system, accessibility of healthcare facilities, and stigma about autism. Further efforts are needed to empower patients, adequately train providers, increase the accessibility of the healthcare system, and decrease discrimination.

Nyquist, P. A., Naval, N. S., & Carhuapoma, J. R. (2009). *Future therapy in intracerebral hemorrhage and intraventricular hemorrhage: Aspiration and thrombolysis* Cambridge University Press.

Introduction Thirty-day mortality after intracerebral hemorrhage (ICH) approaches 50%. Within the surviving patients, only 20% achieve a meaningful level of functional recovery at six months [1,2]. Intraventricular hemorrhage (IVH) is the direct hemorrhage of blood into the ventricles of the brain. Mortality estimates for IVH range from 50% to 80% [3–8]. The most common cause of IVH is spontaneous ICH, followed by subarachnoid hemorrhage (SAH). The incidence of IVH in ICH is about twice that in SAH [7]. Approximately 10% of aneurysmal SAH and 40% of primary ICH experience IVH [7,9,10]. Intraventricular hemorrhage in ICH and SAH account for 10% of the 700,000 strokes occurring yearly in the United States [7,9–11]. The total annual incidence of IVH in the United States is estimated to be about 22,000 adults per year [9]. Case-control cohort studies have repeatedly identified hematoma volume and admission Glasgow Coma Scale [GCS] score to be the main prognostic factors affecting survival and neurological outcome in patients with ICH and IVH [12]. Reduction of hematoma volume in both ICH and IVH could lead to improved neurological outcome by several mechanisms. Reduction of clot size will directly reduce local mass effect, thus decreasing the risk of fatal complications such as brainstem compression. In addition, minimizing hematoma volume could also lead to a decreased risk of globally elevated intracranial pressure (ICP) due to obstructive hydrocephalus (“trapped ventricles”). © J. R. Carhuapoma, S. A. Mayer, and D. F. Hanley 2010.

Oberbeck, D. (2008). Laser-assisted microdissection. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(3), 249-250.

When analyzing alcohol's effects on the brain, researchers often want to look at small clusters of cells that can be studied in isolation from the surrounding brain tissue rather than at the entire brain or larger brain areas. This implies that relatively small numbers of cells have to be retrieved from the brain and studied in culture or subjected to biochemical analyses. The challenge then becomes how to isolate small numbers of cells from a specific brain region without including unwanted cells. One approach to solving this problem is to use a technology known as laser-assisted microdissection (LMD). This article reviews some of the principles of LMD and its use in alcohol research.

O'Glasser, A. Y., & Milas, K. M. (2015). Horner's, heterochromia, and harlequins. *Journal of General Internal Medicine*,

Ojeda, S. R., Lomniczi, A., Sandau, U., & Matagne, V. (2009). *New concepts on the control of the onset of puberty* S. Karger AG.

The initiation of mammalian puberty requires an increased pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This increase is brought about by changes in transsynaptic and glial-neuronal communication. Coordination of these cellular interactions likely requires the participation of sets of genes hierarchically arranged within functionally connected networks. Using high throughput, genetic, molecular and bioinformatics strategies, in combination with a systems biology approach, three transcriptional regulators of the pubertal process have been identified, and the structure of at least one hypothalamic gene network has been proposed. A genomewide analysis of hypothalamic DNA methylation revealed profound changes in methylation patterns associated with the onset of female puberty. Pharmacological disruption of two epigenetic marks associated with gene silencing (DNA methylation and histone deacetylation) resulted in pubertal failure, instead of advancing the onset of puberty, suggesting that disruption of these two silencing mechanisms leads to activation of repressor genes whose expression would normally decrease at puberty. These observations suggest that the genetic underpinnings of puberty are polygenic rather than specified by a single gene, and that epigenetic mechanisms may provide coordination and transcriptional plasticity to this genetic network. © 2010 by S. Karger AG. All rights reserved.

Ortiz, D., Guiguemde, W. A., Johnson, A., Elya, C., Anderson, J., Clark, J., et al. (2015). Identification of selective inhibitors of the plasmodium falciparum hexose transporter PfHT by screening focused libraries of anti-malarial compounds. *PLoS One*, *10*(4), e0123598.

Development of resistance against current antimalarial drugs necessitates the search for novel drugs that interact with different targets and have distinct mechanisms of action. Malaria parasites depend upon high levels of glucose uptake followed by inefficient metabolic utilization via the glycolytic pathway, and the Plasmodium falciparum hexose transporter PfHT, which mediates uptake of glucose, has thus been recognized as a promising drug target. This

transporter is highly divergent from mammalian hexose transporters, and it appears to be a permease that is essential for parasite viability in intra-erythrocytic, mosquito, and liver stages of the parasite life cycle. An assay was developed that is appropriate for high throughput screening against PfHT based upon heterologous expression of PfHT in *Leishmania mexicana* parasites that are null mutants for their endogenous hexose transporters. Screening of two focused libraries of antimalarial compounds identified two such compounds that are high potency selective inhibitors of PfHT compared to human GLUT1. Additionally, 7 other compounds were identified that are lower potency and lower specificity PfHT inhibitors but might nonetheless serve as starting points for identification of analogs with more selective properties. These results further support the potential of PfHT as a novel drug target.

Oster, N. V., Geller, B. M., Carney, P. A., Reisch, L. M., Onega, T., Weaver, D. L., et al. (2015).

Demographic and practice characteristics of pathologists who enjoy breast tissue interpretation. *Breast*, 24(2), 107-111.

Physician attributes, job satisfaction and confidence in clinical skills are associated with enhanced performance and better patient outcomes. We surveyed 252 pathologists to evaluate associations between enjoyment of breast pathology, demographic/clinical characteristics and diagnostic performance. Diagnostic performance was determined by comparing pathologist assessments of a set of 60 cases with consensus assessments of the same cases made by a panel of experienced pathologists. Eighty-three percent of study participants reported enjoying breast pathology. Pathologists who enjoy breast interpretation were more likely to review  $\geq 10$  cases/week (.  $p=0.003$ ), report breast interpretation expertise (.  $p=0.013$ ) and have high levels of confidence interpreting breast pathology (.  $p<0.001$ ). These pathologists were less likely to report that the field was challenging (.  $p<0.001$ ) and that breast cases make them more nervous than other types of pathology (.  $p<0.001$ ). Enjoyment was not associated with diagnostic performance. Millions of women undergo breast biopsy annually, thus it is reassuring that although nearly a fifth of practicing pathologists who interpret breast tissue report not enjoying the field, precision is not impacted. © 2014 Elsevier Ltd.

Ostrowski, K. A., Polackwich, A. S., Kent, J., Conlin, M. J., Hedges, J. C., & Fuchs, E. F. (2015). Higher outcomes of vasectomy reversal in men with the same female partner as before vasectomy. *The Journal of Urology*, 193(1), 245-247.

PURPOSE: We reviewed fertility outcomes of vasectomy reversal at a high surgical volume center in men with the same female partner as before vasectomy. MATERIALS AND METHODS: We retrospectively studied a prospective database. All vasectomy reversals were performed by a single surgeon (EFF). Patients who underwent microsurgical vasectomy reversal and had the same female partner as before vasectomy were identified from 1978 to 2011. Pregnancy and live birth rates, procedure type (bilateral vasovasostomy, bilateral vasoepididymostomy, unilateral vasovasostomy or unilateral vasoepididymostomy), patency rate, time from reversal and spouse age were evaluated. RESULTS: We reviewed the records of 3,135 consecutive microsurgical vasectomy reversals. Of these patients 524 (17%) who underwent vasectomy reversal had the same female partner as before vasectomy. Complete information was available on 258 patients (49%), who had a 94% vas patency rate. The clinical pregnancy rate was 83% by natural means compared to 60% in our general vasectomy reversal population ( $p < 0.0001$ ). On logistic regression analysis controlling for female partner and patient ages, years from vasectomy and vasectomy reversal with the same female partner the OR was 2 ( $p < 0.007$ ). Average time from vasectomy was 5.7 years. Average patient and female partner age at reversal was 38.9 and 33.2 years, respectively. CONCLUSIONS: Outcomes of clinical pregnancy and live birth rates are higher in men who undergo microsurgical vasectomy reversal with the same female partner. These outcomes may be related to a shorter interval from vasectomy, previous fertility and couple motivation.

Ozcan, U. A., Isik, U., Ozpinar, A., Baykan, N., & Dincer, A. (2015). Assessment of sedated pediatric brain with 3D-FLAIR sequence at 3T MRI. *Brain and Development*, 37(5), 495-500.

In sedated pediatric brains, 2D-FLAIR causes increased signal intensity of the cerebrospinal fluid (CSF) leading to false-positive diagnoses. Our aim is to determine whether increased CSF signal intensity is observed on 3D-FLAIR images. Methods: In this institutional review board-approved study, a 2-year retrospective analysis of our MRI database was conducted which revealed 48 sedated pediatric patients with normal cranial MRI findings and 3D-FLAIR sequence. One adult

volunteer was imaged before and after O<sub>2</sub> inhalation with 2D and 3D-FLAIR sequences. The hyperintensity in the subarachnoid spaces and basal cisterns were quantified as follows: 0: artifact free; 1: homogeneous minimal CSF signal; 2: abnormal CSF signal. Inter-observer agreement was assessed with kappa agreement analysis. Results: Grade 0 and grade 1 signals were observed at inferior to Lilliequist membrane (LLQ) in 48/48 and 0/48 cases; prepontine cistern 47/48 and 1/48; superior to LLQ 26/48 and 22/48; 4th ventricle 16/48 and 32/48; 3rd ventricle 34/48 and 14/48; lateral ventricle 3/48 and 45/48; subarachnoid space 36/48 and 12/48, respectively. No patients showed grade 2 signal. Inter-observer agreement was 0.81-1. In the volunteer, after O<sub>2</sub> inhalation, grade 2 signal intensity was evident on 2D-FLAIR however; 3D-FLAIR did not show any signal increase. Conclusions: In sedated pediatric brains, 3D-FLAIR suppresses CSF signal, and enables reliable assessment free from CSF artifacts. © 2014 The Japanese Society of Child Neurology.

Packer, M., Teuma, E. V., Glasser, A., & Bott, S. (2015). Defining the ideal femtosecond laser capsulotomy. *The British Journal of Ophthalmology*,

PURPOSE: We define the ideal anterior capsulotomy through consideration of capsular histology and biomechanics. Desirable qualities include preventing posterior capsular opacification (PCO), maintaining effective lens position (ELP) and optimising capsular strength. METHODS: Laboratory study of capsular biomechanics and literature review of histology and published clinical results. RESULTS: Parameters of ideal capsulotomy construction include complete overlap of the intraocular lens to prevent PCO, centration on the clinical approximation of the optical axis of the lens to ensure concentricity with the capsule equator, and maximal capsular thickness at the capsulotomy edge to maintain integrity. CONCLUSIONS: Constructing the capsulotomy centred on the clinical approximation of the optical axis of the lens with diameter 5.25 mm optimises prevention of PCO, consistency of ELP and capsular strength.

Palejwala, N. V., Stempel, A. J., & Stout, J. T. (2015). Bilateral giant retinal tears in a pediatric patient with leukemia inhibitory factor receptor deficiency (stuve-wiedemann syndrome). *Retinal Cases & Brief Reports*,

PURPOSE: To describe a case of retinal detachment in a patient with Stuve-Wiedemann

syndrome. METHODS: This report is a retrospective observational case report. The patient's demographics include age, gender, and race, as well as visual acuity, ophthalmic examination, and surgical intervention were extracted from the medical record. For immunohistochemistry studies, a sample of normal human retina from an enucleated specimen was obtained from the Pathology laboratory. A leukemia inhibitory factor receptor/CD118 antibody was obtained from Santa Cruz Biotechnology. RESULTS: A 13-year-old Hispanic boy with known history of Stuve-Wiedemann syndrome (confirmed by genetic testing) presented with bilateral rhegmatogenous retinal detachments secondary to bilateral giant retinal tears. He underwent multiple surgical repairs in both eyes, resulting in successful reattachment in the right eye and an intractable closed funnel detachment in the left eye. CONCLUSION: This is the first case of vitreoretinal pathology reported in Stuve-Wiedemann syndrome. Using immunohistochemistry staining, the authors found ubiquitous expression of leukemia inhibitory factor receptor protein in the normal human retina. They hypothesize that leukemia inhibitory factor receptor mutation may cause intrinsic weakness of the neurosensory retina predisposing it to injury.

Parekh, R. S., Meoni, L. A., Jaar, B. G., Sozio, S. M., Shafi, T., Tomaselli, G. F., et al. (2015).

Rationale and design for the predictors of arrhythmias and cardiovascular disease in end stage renal disease (PACE) study. *BMC Nephrology*, 16(1), 63.

BACKGROUND: Sudden cardiac death occurs commonly in the end-stage renal disease population receiving dialysis, with 25% dying of sudden cardiac death over 5 years. Despite this high risk, surprisingly few prospective studies have studied clinical- and dialysis-related risk factors for sudden cardiac death and arrhythmic precursors of sudden cardiac death in end-stage renal disease. METHODS/DESIGN: We present a brief summary of the risk factors for arrhythmias and sudden cardiac death in persons with end-stage renal disease as the rationale for the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease (PACE), a prospective cohort study of patients recently initiated on chronic hemodialysis, with the overall goal to understand arrhythmic and sudden cardiac death risk. Participants were screened for eligibility and excluded if they already had a pacemaker or an automatic implantable cardioverter defibrillator. We describe the study aims, design and data collection of 574 incident hemodialysis participants from the Baltimore region in Maryland, U.S.A.. Participants were recruited from 27 hemodialysis units

and underwent detailed clinical, dialysis and cardiovascular evaluation at baseline and follow-up. Cardiovascular phenotyping was conducted on nondialysis days with signal averaged electrocardiogram, echocardiogram, pulse wave velocity, ankle brachial index and cardiac computed tomography and angiography conducted at baseline. Participants were followed annually with study visits including electrocardiogram, pulse wave velocity and ankle brachial index up to 4 years. A biorepository of serum, plasma, DNA, RNA and nails were collected to study genetic and serologic factors associated with disease. DISCUSSION: Studies of modifiable risk factors for sudden cardiac death will help set the stage for clinical trials to test therapies to prevent sudden cardiac death in this high-risk population.

Passias, P. G., Soroceanu, A., Scheer, J., Yang, S., Boniello, A., Smith, J. S., et al. (2015). Magnitude of preoperative cervical lordotic compensation and C2-T3 angle are correlated to increased risk of post-operative sagittal spinal pelvic malalignment in adult thoracolumbar deformity patients at 2-year follow-up. *The Spine Journal : Official Journal of the North American Spine Society*,

BACKGROUND CONTEXT: Cervical Deformity (CD) is prevalent among patients with adult spinal deformity (ASD). The effect of baseline cervical alignment on achieving optimal thoracolumbar alignment in ASD surgery is unclear. PURPOSE: This study assesses the relationship between pre-operative cervical spinal parameters and global alignment following thoracolumbar ASD surgery at 2-year follow up. STUDY DESIGN/SETTING: A retrospective review of a multi-center, prospective database. PATIENT SAMPLE: Surgical ASD patients with 2-year follow-up and cervical x-rays. OUTCOME MEASURES: The outcome measure was radiographic parameters and self-reported HRQL measures (SF-36, ODI and SRS-22). METHODS: Surgical ASD patients over the age of 18 with scoliosis  $\geq 20$  degrees and one of the following radiographic parameters were included: SVA  $\geq 5$ cm, pelvic tilt  $\geq 25$  degrees or thoracic kyphosis  $> 60$  degrees . SRS-Schwab sagittal modifiers (PT, GA, PI-LL) were assessed at 2-year post-op as either normal ("0") or abnormal ("+" or "++"). Patients were classified in the Aligned Group (AG) or Malaligned Group (MG) at 2-year follow-up if all 3 sagittal modifiers were normal or abnormal, respectively. Patients were assessed for CD based on the following criteria: C2-C7 SVA  $> 4$ cm, C2-C7 SVA 0), cervical lordosis (CL 4cm OR CL  $> 0$ ), and both CD (C2-C7 SVA  $> 4$ cm AND CL  $> 0$ ). Univariate testing was performed using t-tests or chi square, looking at the following pre-op parameters:

CD, C2-C7 SVA, C2-T3 SVA, CL, T1S, T1S-CL, C2-T3 angle, LL, TK, PT, C7-S1 SVA, and PI-LL. No study funding sources are related to this clinical study. The International Spine Study Group (ISSG) is funded through research grants from DePuy-Synthes and individual donations.

RESULTS: 104 patients met initial inclusion criteria with 70 in the AG group and 34 in MG. Pre-op, patients in the MG group had a higher cervical lordosis (11.7 vs 4.9,  $p=0.03$ ), higher C2-T3 angle (13.59 vs 4.9  $p=0.01$ ), higher PT ( $p<0.0001$ ), higher SVA ( $p<0.0001$ ), and higher PI-LL ( $p<0.0001$ ) compared to the AG group. Interestingly, the prevalence of CD at baseline was similar for both groups. There was no statistically significant difference among groups in the amount of improvement over 2 years on the ODI or the SF-36 PCS. CONCLUSIONS: Patients with sagittal spinal mal-alignment associated with significant cervical compensatory lordosis are at increased risk of realignment failure at 2 year follow up. Assessment of the degree of cervical compensation may be helpful in preoperative evaluation to assist in realignment outcome prediction.

Payne, T. H., Hines, L. E., Chan, R. C., Hartman, S., Kapusnik-Uner, J., Russ, A. L., et al. (2015).

Recommendations to improve the usability of drug-drug interaction clinical decision support alerts. *Journal of the American Medical Informatics Association : JAMIA*,

OBJECTIVE: To establish preferred strategies for presenting drug-drug interaction (DDI) clinical decision support alerts. MATERIALS AND METHODS: A DDI Clinical Decision Support Conference Series included a workgroup consisting of 24 clinical, usability, and informatics experts representing academia, health information technology (IT) vendors, healthcare organizations, and the Office of the National Coordinator for Health IT. Workgroup members met via web-based meetings 12 times from January 2013 to February 2014, and two in-person meetings to reach consensus on recommendations to improve decision support for DDIs. We addressed three key questions: (1) what, how, where, and when do we display DDI decision support? (2) should presentation of DDI decision support vary by clinicians? and (3) how should effectiveness of DDI decision support be measured? RESULTS: Our recommendations include the consistent use of terminology, visual cues, minimal text, formatting, content, and reporting standards to facilitate usability. All clinicians involved in the medication use process should be able to view DDI alerts and actions by other clinicians. Override rates are common but may not be a good measure of

effectiveness. DISCUSSION: Seven core elements should be included with DDI decision support. DDI information should be presented to all clinicians. Finally, in their current form, override rates have limited capability to evaluate alert effectiveness. CONCLUSION: DDI clinical decision support alerts need major improvements. We provide recommendations for healthcare organizations and IT vendors to improve the clinician interface of DDI alerts, with the aim of reducing alert fatigue and improving patient safety.

Peacock, F., Beckley, P., Clark, C., Disch, M., Hewins, K., Hunn, D., et al. (2014). Recommendations for the evaluation and management of observation services: A consensus white paper: The society of cardiovascular patient care. *Critical Pathways in Cardiology*, 13(4), 163-198.

Observation Services (OS) was founded by emergency physicians in an attempt to manage "boarding" issues faced by emergency departments throughout the United States. As a result, OS have proven to be an effective strategy in reducing costs and decreasing lengths of stay while improving patient outcomes. When OS are appropriately leveraged for maximum efficiency, patients presenting to emergency departments with common disease processes can be effectively treated in a timely manner. A wellstructured observation program will help hospitals reduce the number of inappropriate, costly inpatient admissions while avoiding the potential of inappropriate discharges. Observation medicine is a complicated multidimensional issue that has generated much confusion. This service is designed to provide the best possible patient care in a value-based purchasing environment where quality, cost, and patient satisfaction must continually be addressed. Observation medicine is a service not a status. Therefore, patients are admitted to the service as outpatients no matter whether they are placed in a virtual or dedicated observation unit. The key to a successful observation program is to determine how to maximize efficiencies. This white paper provides the reader with the foundational guidance for observational services. It defines how to set up an observational service program, which diagnoses are most appropriate for admission, and what the future holds. The goal is to help care providers from any hospital deliver the most appropriate level of treatment, to the most appropriate patient, in the most appropriate location while controlling costs. Copyright © 2014 by Lippincott Williams & Wilkins.

Peña, Z. G., Sivamani, R. K., Konia, T. H., & Eisen, D. B. (2015). Squamous cell carcinoma in the setting of chronic hidradenitis suppurativa; report of a patient and update of the literature. *Dermatology Online Journal*, 21(4)

Squamous cell carcinoma (SCC) developing in chronic hidradenitis suppurativa (HS) is rare, but failing to recognize the condition may have significant consequences. Dermatologists must be aware of the potential for malignant transformation and should have a low threshold for biopsy when clinical presentation is atypical. Herein we describe a 64-year-old woman with metastatic vulvar SCC that developed within an area of chronic HS. Like SCC associated with other chronic inflammatory disorders (Marjolin's ulcers), mortality is significant. Past reviews have reported death rates above 40% and our most recent update continues to support poor prognoses for these patients. 2015 by the article author(s)

Perry, K. A., Pham, T. H., Spechler, S. J., Hunter, J. G., Melvin, W. S., & Velanovich, V. (2015). 2014 SSAT state-of-the-art conference: Advances in diagnosis and management of gastroesophageal reflux disease. *Journal of Gastrointestinal Surgery*, 19(3), 458-466.

Gastroesophageal reflux disease affects at least 10 % of people in Western societies and produces troublesome symptoms and impairs patients' quality of life. The effective management of GERD is imperative as the diagnosis places a significant cost burden on the United States healthcare system with annual direct cost estimates exceeding 9 billion dollars annually. While effective for many patients, 30–40 % of patients receiving medical therapy with proton pump inhibitors experience troublesome breakthrough symptoms, and recent evidence suggests that this therapy subjects patients to increased risk of complications. Given the high cost of PPI therapy, patients are showing a decrease in willingness to continue with a therapy that provides incomplete relief; however, due to inconsistent outcomes and concern for procedure-related side effects following surgery, only 1 % of the GERD population undergoes anti-reflux surgery annually. The discrepancy between the number of patients who experience suboptimal medical treatment and the number considered for anti-reflux surgery indicates a large therapeutic gap in the management of GERD. The objective of the SSAT State-of-the-Art Conference was to examine technologic advances in the diagnosis and treatment of GERD and to evaluate the ways

in which we assess the outcomes of these therapies to provide optimal patient care. © 2014, The Society for Surgery of the Alimentary Tract.

Peters, A., Verma, K., Slobodyanyuk, K., Cheriyan, T., Hoelscher, C., Schwab, F., et al. (2015).

Antifibrinolytics reduce blood loss in adult spinal deformity surgery: A prospective, randomized controlled trial. *Spine*, 40(8), E443-9.

STUDY DESIGN: This is a prospective, randomized, double-blinded comparison of tranexamic acid (TXA), epsilon aminocaproic acid (EACA), and placebo used intraoperatively in patients with adult spinal deformity. OBJECTIVE: The purpose of this study was to provide high-quality evidence regarding the comparative efficacies of TXA, EACA, and placebo in reducing blood loss and transfusion requirements in patients undergoing posterior spinal fusion surgery. SUMMARY OF BACKGROUND DATA: Spine deformity surgery usually involves substantial blood loss. The antifibrinolytics TXA and EACA have been shown to improve hemostasis in large blood loss surgical procedures. METHODS: Fifty-one patients undergoing posterior spinal fusion of at least 5 levels for correction of adult spinal deformity were randomized to 1 of 3 treatment groups. Primary outcome measures included intraoperative estimated blood loss, total loss, (estimated blood loss + postoperative blood loss), and transfusion rates. RESULTS: Patients received TXA (n = 19), EACA (n = 19), or placebo (n = 13) in the operating room (mean ages: 60, 47, and 43 yr, respectively); TXA patients were significantly older and had larger estimated blood volumes than both other groups. Total losses were significantly reduced for EACA versus control, and there was a demonstrable but nonsignificant trend toward reduced intraoperative blood loss in both antifibrinolytic arms versus control. EACA had significant reductions in postoperative blood transfusions versus TXA. CONCLUSION: The findings in this study support the use of antifibrinolytics to reduce blood loss in posterior adult spinal deformity surgery. LEVEL OF EVIDENCE: 1.

Posielski, N. M., Yee, S. T., Majumder, A., Orenstein, S. B., Prabhu, A. S., & Novitsky, Y. W. (2015).

Repair of massive ventral hernias with "quilted" mesh. *Hernia*,

Introduction: Prosthetic reinforcement is a critical component of hernia repair. For massive defects, mesh overlap is often limited by the dimensions of commercially available implants. In

scenarios where larger mesh prosthetics are required for adequate reinforcement, it may be necessary to join several pieces of mesh together using non-absorbable suture. Here, we report our outcomes for abdominal wall reconstructions in which “quilted” mesh was utilized for fascial reinforcement. Methods: Patients undergoing open incisional hernia repair utilizing posterior component separation and transversus abdominis muscle release, with use of quilted synthetic mesh placed in the retromuscular position, were reviewed. Main outcome measures included patient, hernia, and operative characteristics and post-operative outcomes, including surgical site occurrence (SSO), surgical site infection (SSI), and recurrence. Results: Thirty-two patients (mean age  $55.7 \pm 9.3$ , BMI  $38.3 \pm 5.8$  kg/m<sup>2</sup>) underwent open ventral hernia repair with “quilted” mesh placed in the retromuscular position. The mean defect area was  $760.1 \pm 311.0$  cm<sup>2</sup> with a mean width of  $24.7 \pm 6.4$  cm. Quilted meshes consisted of two-piece (69 %), three-piece (19 %) and four-piece (12 %) configurations. Wound morbidity consisted of eight (25 %) SSOs, including four (13 %) SSIs, all of which resolved without mesh excision. With mean follow-up of  $9.0 \pm 13.6$  months, there were two (6.3 %) lateral recurrences, both unassociated with mesh-to-mesh suture line failure. Conclusions: Massive ventral hernias that require giant mesh prosthetics, currently not commercially available, may be successfully repaired using multiple mesh pieces sewn together in a quilt-like fashion. Such retromuscular repairs are durable, without added morbidity due to the mesh-to-mesh suture line. However, additional operative time is required for quilting the mesh together, prompting strong calls for manufacturing of larger mesh prosthetics. © 2015 Springer-Verlag France

Postow, M. A., Chesney, J., Pavlick, A. C., Robert, C., Grossmann, K., McDermott, D., et al. (2015).

Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *The New England Journal of Medicine*,

Background In a phase 1 dose-escalation study, combined inhibition of T-cell checkpoint pathways by nivolumab and ipilimumab was associated with a high rate of objective response, including complete responses, among patients with advanced melanoma. Methods In this double-blind study involving 142 patients with metastatic melanoma who had not previously received treatment, we randomly assigned patients in a 2:1 ratio to receive ipilimumab (3 mg per kilogram of body weight) combined with either nivolumab (1 mg per kilogram) or placebo once

every 3 weeks for four doses, followed by nivolumab (3 mg per kilogram) or placebo every 2 weeks until the occurrence of disease progression or unacceptable toxic effects. The primary end point was the rate of investigator-assessed, confirmed objective response among patients with BRAF V600 wild-type tumors. Results Among patients with BRAF wild-type tumors, the rate of confirmed objective response was 61% (44 of 72 patients) in the group that received both ipilimumab and nivolumab (combination group) versus 11% (4 of 37 patients) in the group that received ipilimumab and placebo (ipilimumab-monotherapy group) ( $P < 0.001$ ), with complete responses reported in 16 patients (22%) in the combination group and no patients in the ipilimumab-monotherapy group. The median duration of response was not reached in either group. The median progression-free survival was not reached with the combination therapy and was 4.4 months with ipilimumab monotherapy (hazard ratio associated with combination therapy as compared with ipilimumab monotherapy for disease progression or death, 0.40; 95% confidence interval, 0.23 to 0.68;  $P < 0.001$ ). Similar results for response rate and progression-free survival were observed in 33 patients with BRAF mutation-positive tumors. Drug-related adverse events of grade 3 or 4 were reported in 54% of the patients who received the combination therapy as compared with 24% of the patients who received ipilimumab monotherapy. Select adverse events with potential immunologic causes were consistent with those in a phase 1 study, and most of these events resolved with immune-modulating medication. Conclusions The objective-response rate and the progression-free survival among patients with advanced melanoma who had not previously received treatment were significantly greater with nivolumab combined with ipilimumab than with ipilimumab monotherapy. Combination therapy had an acceptable safety profile. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT01927419 .).

Proskocil, B. J., Bruun, D. A., Garg, J. A., Villagomez, C. C., Jacoby, D. B., Lein, P. J., et al. (2015).

Sensitization can influence mechanisms of organophosphorus pesticide-induced airway hyperreactivity. *American Journal of Respiratory Cell and Molecular Biology*,

We previously demonstrated that antigen sensitization increases vulnerability to airway hyperreactivity induced by the organophosphorus pesticide (OP) parathion. Sensitization also changes the mechanism of parathion-induced airway hyperreactivity to one that is dependent on

interleukin-5 (IL5). To determine whether this effect can be generalized to other OPs, and to other classes of pesticides, we measured airway responsiveness to vagal stimulation or intravenous acetylcholine in non-sensitized and ovalbumin-sensitized guinea pigs 24 h after a single subcutaneous injection of the OPs diazinon or chlorpyrifos or the pyrethroid permethrin. Sensitization exacerbated the effects of chlorpyrifos on bronchoconstriction in response to vagal stimulation or i.v. acetylcholine. Pretreatment with function-blocking IL5 antibody prevented chlorpyrifos-induced airway hyperreactivity in sensitized but not in non-sensitized guinea pigs. In sensitized guinea pigs, blocking IL5 decreased eosinophil activation as measured by decreased eosinophil major basic protein (MBP) in the trachea. In contrast, sensitization did not alter diazinon-induced airway hyperreactivity, and permethrin did not cause airway hyperreactivity in either non-sensitized or sensitized guinea pigs. None of the pesticides affected inflammatory cells in the bronchoalveolar lavage or blood. We have previously shown that 3 different OPs cause airway hyperreactivity via loss of neuronal M2 muscarinic receptor function. Similar to parathion, but unlike diazinon, the mechanism of chlorpyrifos-induced airway hyperreactivity is changed by sensitization. Thus OP-induced airway hyperreactivity is dependent on sensitization status and on the OP used, which may influence therapeutic approaches.

Pruitt, L. D., Luxton, D. D., & Shore, P. (2014). Additional clinical benefits of home-based telemental health treatments. *Professional Psychology: Research and Practice, 45*(5), 340-346.

Home-based telemental health (HBTMH) has several important benefits for both patients and clinical practitioners including improved access to services, convenience, flexibility, and potential cost savings. HBTMH also has the potential to offer additional clinical benefits that are not realized with traditional in-office alternatives. Through a review of the empirical literature, this article presents and evaluates evidence of the clinical benefits and limitations of HBTMH. Particular topics include treatment attendance and satisfaction, social support, access to contextual information, patient and practitioner safety, and concerns about privacy and stigma. By making use of commonly available communication technologies, HBTMH affords opportunities to bridge gaps in care to meet current and future mental health care needs. © 2014 American Psychological Association.

Puhalla, S., Elmquist, W., Freyer, D., Kleinberg, L., Adkins, C., Lockman, P., et al. (2015).

Unsanctifying the sanctuary: Challenges and opportunities with brain metastases. *Neuro-Oncology*, 17(5), 639-651.

While the use of targeted therapies, particularly radiosurgery, has broadened therapeutic options for CNS metastases, patients respond minimally and prognosis remains poor. The inability of many systemic chemotherapeutic agents to penetrate the blood-brain barrier (BBB) has limited their use and allowed brain metastases to become a burgeoning clinical challenge. Adequate preclinical models that appropriately mimic the metastatic process, the BBB, and blood-tumor barriers (BTB) are needed to better evaluate therapies that have the ability to enhance delivery through or penetrate into these barriers and to understand the mechanisms of resistance to therapy. The heterogeneity among and within different solid tumors and subtypes of solid tumors further adds to the difficulties in determining the most appropriate treatment approaches and methods of laboratory and clinical studies. This review article discusses therapies focused on prevention and treatment of CNS metastases, particularly regarding the BBB, and the challenges and opportunities these therapies present.

Qaseem, A., Humphrey, L. L., Harris, R., Starkey, M., & Denberg, T. D. (2015). Screening pelvic examinations in asymptomatic, average-risk adult women: An evidence report for a clinical practice guideline from the American College of Physicians. *Obstetrical and Gynecological Survey*, 69(10), 596-597.

Quinn, G. P., Block, R. G., Clayman, M. L., Kelvin, J., Arvey, S. R., Lee, J. -, et al. (2015). If you did not document it, it did not happen: Rates of documentation of discussion of infertility risk in adolescent and young adult oncology patients' medical records. *Journal of Oncology Practice*, 11(2), 137-144.

Purpose: The adolescent and young adult (AYA) population is underserved because of unique late-effect issues, particularly future fertility. This study sought to establish rates of documentation of discussion of risk of infertility, fertility preservation (FP) options, and referrals to fertility specialists in AYA patients' medical records at four cancer centers. Methods: All centers reviewed randomized records within the top four AYA disease sites (breast, leukemia/lymphoma,

sarcoma, and testicular). Eligible records included those of patients: diagnosed in 2011, with no prior receipt of gonadotoxic therapy; age 18 to 45 years; with no multiple primary cancers; and for whom record was not second opinion. Quality Oncology Practice Initiative methods were used to evaluate documentation of discussion of risk of infertility, discussion of FP options, and referral to a fertility specialist. Results: Of 231 records, 26% documented infertility risk discussion, 24% documented FP option discussion, and 13% documented referral to a fertility specialist. Records were less likely to contain evidence of infertility risk and FP option discussions for female patients ( $P = .030$  and  $.004$ , respectively) and those with breast cancer ( $P = .021$  and  $< .001$ , respectively). Records for Hispanic/Latino patients were less likely to contain evidence of infertility risk discussion ( $P = .037$ ). Records were less likely to document infertility risk discussion, FP option discussion, and fertility specialist referral for patients age  $\geq 40$  years ( $P < .001$ ,  $< .001$ , and  $.002$ , respectively) and those who already had children (all  $P < .001$ ). Conclusion: The overall rate of documentation of discussion of FP is low, and results show disparities among specific groups. Although greater numbers of discussions may be occurring, there is a need to create interventions to improve documentation. Copyright © 2014 by American Society of Clinical Oncology.

Qureshi, W. T., Nasir, K., Hacıoglu, Y., Sibley, C. T., Gupta, M., Rivera, J. J., et al. (2015).

Determination and distribution of left ventricular size as measured by noncontrast CT in the multi-ethnic study of atherosclerosis. *Journal of Cardiovascular Computed Tomography*, 9(2), 113-119.

BACKGROUND: Left ventricular (LV) volume and mass have prognostic relevance. Overall size of the left ventricle as it appears in noncontrast CT is a composite of the ventricular volume and myocardial mass. We describe a method to estimate the LV size using a single cross-section in noncontrast CT and determined normal ranges on the basis of a large population cohort.

METHODS: The Multi-Ethnic Study of Atherosclerosis with 6814 participants from 4 ethnicities who were free of known cardiovascular disease and enrolled between 2000 and 2002 form the basis of our analysis. LV size was calculated from a single cross-sectional slice obtained by either nonenhanced electron beam or multidetector CT. LV size was adjusted to body surface area to obtain the LV size index, which was adjusted for age, sex, race or ethnicity, hypertension,

hyperlipidemia, and diabetes. RESULTS: There were significant differences in LV size index by race which were further influenced by age and sex. Higher values were noted in men in all ethnic groups across all age groups. Similarly, LV size index uniformly decreased with age across all ethnic and sex categories. Caucasians had the lowest and African Americans had the highest LV size index across all age and sex categories. In multivariate regression analyses adjusted for age, sex, race or ethnicity, hypertension, hyperlipidemia, smoking, and diabetes mellitus, the significant differences were noted between male vs female (median difference, 17.5 cc/m<sup>2</sup>; P < .001), ethnic groups (Caucasian, reference group; Asian, 3.7 cc/m<sup>2</sup>; African American, 8.3 cc/m<sup>2</sup>; and Hispanic, 5.6 cc/m<sup>2</sup>; P < .001), and age groups (45-54 years, reference group; 55-64 years, -5.2 cc/m<sup>2</sup>; 65-74 years, -11.4 cc/m<sup>2</sup>; and 74-84 years, -12.5 cc/m<sup>2</sup>). CONCLUSIONS: This study provides normative values for LV size as determined from a single, nonenhanced CT cross-section and indexed to body surface area, and it demonstrates that the LV size index varies by age, sex, and ethnic background.

Raess, P. W., Habashi, A., El Rassi, E., Milas, M., Sauer, D. A., & Troxell, M. L. (2015). Overlapping morphologic and immunohistochemical features of hashimoto thyroiditis and IgG4-related thyroid disease. *Endocrine Pathology*,

Immunoglobulin G4-related disease (IgG4-RD) is an emerging clinicopathologic entity characterized by both IgG4+ plasma cell infiltration and fibrosis in one or more organs, prototypically pancreas or salivary/lacrimal glands. IgG4-RD in the thyroid (IgG4-RTD) is an area of active study, and the relationship between IgG4-RTD and Hashimoto thyroiditis is not fully delineated due to their overlapping histologic features. Retrospective review was performed of all thyroidectomy cases demonstrating lymphocytic inflammation at a single institution over a 4-year period. Approximately half (23/38) of patients had a clinical diagnosis of Hashimoto thyroiditis (HT). Nine of the 38 patients had increased absolute and relative numbers of IgG4+ plasma cells. Patients with a clinical diagnosis of HT had increased lymphoplasmacytic inflammation, but the relative proportion of IgG4+ plasma cells was not increased compared to patients without HT. There was no correlation between IgG4 levels and the amount of fibrosis in patients with or without HT. Patients identified as having the fibrosing variant of HT were not more likely to have increased levels of IgG4+ plasma cells than those without. There is significant morphologic and

immunohistochemical overlap between HT and IgG4-RTD. Future studies to identify specific characteristics of IgG4-RTD involving the thyroid are necessary to accurately define this entity.

Ramamoorthy, S., Zhang, Y., Petrie, T., Fridberger, A., Ren, T., Wang, R., et al. (2015). Two dimensional vibrations of the guinea pig apex organ of Corti measured in vivo using phase sensitive Fourier domain optical coherence tomography. *Photonic Therapeutics and Diagnostics XI*, , 9303.

In this study, we measure the in vivo apical-turn vibrations of the guinea pig organ of Corti in both axial and radial directions using phase-sensitive Fourier domain optical coherence tomography. The apical turn in guinea pig cochlea has best frequencies around 100 - 500 Hz which are relevant for human speech. Prior measurements of vibrations in the guinea pig apex involved opening the otic capsule, which has been questioned on the basis of the resulting changes to cochlear hydrodynamics. Here this limitation is overcome by measuring the vibrations through bone without opening the otic capsule. Furthermore, we have significantly reduced the surgery needed to access the guinea pig apex in the axial direction by introducing a miniature mirror inside the bulla. The method and preliminary data are discussed in this article.

Raslan, A., & Bhardwaj, A. (2009). *Cerebral edema and intracranial pressure* Cambridge University Press.

Cerebral edema is a frequent and challenging problem in the clinical setting and is a major cause of morbidity and mortality in patients with acute brain injury. It is simply defined as an increase in brain water content (normal brain water content is approximately 80%) and is invariably a consequence of a primary brain insult. Etiologies of these neurologic injuries that cause cerebral edema are diverse and commonly include: Traumatic brain injury (TBI) Subarachnoid hemorrhage (SAH) Ischemic stroke Intracerebral hemorrhage (ICH) Neoplasms (primary and metastatic) Inflammatory diseases (meningitis, ventriculitis, cerebral abscess, encephalitis) • Toxic-metabolic derangements (hyponatremia, fulminant hepatic encephalopathy) CEREBRAL EDEMA: CLASSIFICATION Traditional classification of cerebral edema into cytotoxic, vasogenic, and interstitial (hydrocephalic) is overly simplistic in that it does not reflect the complexity of pathophysiologic and underlying molecular mechanisms. However, it serves as a simple

therapeutic guide. Cytotoxic edema results from swelling of the cellular elements (neurons, glia, and endothelial cells) because of substrate and energy (Na<sup>+</sup>, K<sup>+</sup> pump) failure and affects both gray and white matter. This edema subtype is the initial accompaniment of any brain injury irrespective of etiology and conventionally is thought to be resistant to any known medical treatment. Vasogenic edema that predominantly affects white matter, typically encountered in TBI, neoplasms, and inflammatory conditions, results from breakdown of the blood-brain barrier (BBB) due to increased vascular permeability and consequent leakage of plasma components. This edema subtype is responsive to both steroids (notably edema associated with neoplasms) and osmotherapy.[...] © Cambridge University Press 2010.

Reed, K. L., & Okundaye, A. J. (2014). *Management of emergencies associated with pediatric dental sedation* Wiley Blackwell.

Medical emergencies, sometimes life-threatening, can and do occur in the pediatric dental office. The focus of this chapter is on the management of medical emergencies directly associated with pediatric sedation. The basic algorithm for the management of most medical emergencies is: (P) position, (A) airway, (B) breathing, (C) circulation, and (D) definitive care: differential diagnosis, drugs, defibrillation. The algorithm is discussed in detail in the chapter, as it relates to pediatric dental sedation. Children present the highest risk and lowest error tolerance in patient safety during sedation procedures. Familiarity with the patient's medical history is highly important in preventing medical emergencies. Management of medical emergencies in the dental office may be limited to supporting a patient's vital functions until emergency medical services (EMS) arrive, especially in the case of major morbidity. © 2014 by John Wiley & Sons, Inc.

Reed, K. L., & Okundaye, A. J. (2014). *Working with a dentist anesthesiologist* Wiley Blackwell.

Anesthesia and dental services may be delivered in a dental office at significantly lower costs than in the hospital operating room. There now is a trend toward in-office deep sedation and general anesthetics in some geographical regions. This chapter focuses on the reason for that trend, as well as how to work with a dentist anesthesiologist. The spread between hospital-based anesthesia and dental office-based anesthesia pricing still exists today. Dentist anesthesiologists can help pediatric dentists with their more troublesome patients by allowing dentistry to be

completed safely in a cost-effective manner. There are different techniques for inducing and maintaining deep sedation and general anesthesia, different airway adjuncts that may be chosen, different drugs that may be used for maintaining deep sedation and general anesthesia, and different ways of recovering the pediatric dental patient from deep sedation or general anesthesia. © 2014 by John Wiley & Sons, Inc.

Rich, N. E., Sanders, C., Hughes, R. S., Fontana, R. J., Stravitz, R. T., Fix, O., et al. (2015). Malignant infiltration of the liver presenting as acute liver failure. *Clinical Gastroenterology and Hepatology*, 13(5), 1025-1028.

There have been few reports of acute liver failure (ALF), with encephalopathy and coagulopathy, caused by infiltration of the liver by malignant cells. We describe a case series of 27 patients with ALF caused by malignancy. We examined a large, multicenter ALF registry (1910 patients; mean age, 47.1 ± 13.9 y) and found only 27 cases (1.4%) of ALF attributed to malignancy. Twenty cases (74%) presented with abdominal pain and 11 presented with ascites. The most common malignancies included lymphoma or leukemia (33%), breast cancer, (30%), and colon cancer (7%); 90% of the patients with lymphoma or leukemia had no history of cancer, compared with 25% of patients with breast cancer. Overall, 44% of the patients had evidence of liver masses on imaging. Diagnosis was confirmed by biopsy in 15 cases (55%) and by autopsy for 6 cases. Twenty-four patients (89%) died within 3 weeks of ALF. © 2015 AGA Institute.

Riddle, M. C., Yki-Jarvinen, H., Bolli, G. B., Ziemien, M., Muehlen-Bartmer, I., Cissokho, S., et al. (2015). One year sustained glycaemic control and less hypoglycaemia with new insulin glargine 300 U/mL compared with 100 U/mL in people with type 2 diabetes using basal + meal-time insulin (EDITION 1 12-month randomized trial including 6-month extension). *Diabetes, Obesity & Metabolism*,  
AIMS: To evaluate maintenance of efficacy and safety of insulin glargine 300 U/mL (Gla-300) versus glargine 100 U/mL (Gla-100) in people with type 2 diabetes mellitus using basal plus meal-time insulin for 12 months in EDITION 1. MATERIALS AND METHODS: EDITION 1 was a multicentre, randomized, open-label, two-arm, phase 3a study. Participants completing the initial 6-month treatment period continued to receive Gla-300 or Gla-100, as previously randomized,

once daily for a further 6-month open-label extension phase. Change in HbA1c , fasting plasma glucose, insulin dose, hypoglycaemic events and body weight were assessed. RESULTS: Of 807 participants enrolled in the initial phase, 89% (359/404) assigned to Gla-300 and 88% (355/403) to Gla-100 completed 12 months. Glycaemic control was sustained in both groups (mean HbA1c Gla-300, 7.24 %; Gla-100, 7.42 %), with more sustained HbA1c reduction for Gla-300 at 12 months (least squares mean difference Gla-300 versus Gla-100: HbA1c -0.17 [95% CI: -0.30 to -0.05] %). Mean daily basal insulin dose at 12 months was 1.03 U/kg for Gla-300 and 0.90 U/kg with Gla-100. Lower percentages of participants had  $\geq 1$  confirmed ( $\leq 3.9$  mmol/L [ $\leq 70$  mg/dL]) or severe hypoglycaemic event with Gla-300 than Gla-100 at any time of day (24 h) (86% versus 92%; relative risk [RR] 0.94 [95% CI: 0.89 to 0.99]) and during the night (54% versus 65%; RR 0.84 [0.75 to 0.94]), while the annualized rates of such hypoglycaemic events were comparable. No between-treatment differences in adverse events were apparent.

CONCLUSION: During 12 months of treatment of type 2 diabetes requiring basal and meal-time insulin, glycaemic control was better sustained and fewer individuals reported hypoglycaemia with Gla-300 than Gla-100. The mean basal insulin dose was higher with Gla-300 compared with Gla-100, but total numbers of hypoglycaemic events and overall tolerability did not differ between treatments.

Rosenbaum, J. T., Choi, D., Wilson, D. J., Grossniklaus, H. E., Harrington, C. A., Sibley, C. H., et al.

(2015). Parallel gene expression changes in sarcoidosis involving the lacrimal gland, orbital tissue, or blood. *JAMA Ophthalmology*,

Importance: Sarcoidosis is a major cause of ocular or periocular inflammation. The pathogenesis of sarcoidosis is incompletely understood and diagnosis often requires a biopsy. Objective: To determine how gene expression in either orbital adipose tissue or the lacrimal gland affected by sarcoidosis compares with gene expression in other causes of orbital disease and how gene expression in tissue affected by sarcoidosis compares with gene expression in peripheral blood samples obtained from patients with sarcoidosis. Design, Setting, and Participants: In a multicenter, international, observational study, gene expression profiling of formalin-fixed biopsy specimens, using GeneChipp U133 Plus 2 microarrays (Affymetrix), was conducted between October 2012 and January 2014 on tissues biopsied from January 2000 through June 2013.

Participants included 12 patients with orbital sarcoidosis (7 in adipose tissue; 5 affecting the lacrimal gland) as well as comparable tissue from 6 healthy individuals serving as controls or patients with thyroid eye disease, nonspecific orbital inflammation, or granulomatosis with polyangiitis. In addition, results were compared with gene expression in peripheral blood samples obtained from 12 historical individuals with sarcoidosis. Main Outcomes and Measures: Significantly differentially expressed transcripts defined as a minimum of a 1.5-fold increase or a comparable decrease and a false discovery rate of  $P < .05$ . Results: Signals from 2449 probe sets (transcripts from approximately 1522 genes) were significantly increased in the orbital adipose tissue from patients with sarcoidosis. Signals from 4050 probe sets (approximately 2619 genes) were significantly decreased. Signals from 3069 probe sets (approximately 2001 genes) were significantly higher and 3320 (approximately 2283 genes) were significantly lower in the lacrimal gland for patients with sarcoidosis. Ninety-two probe sets (approximately 69 genes) had significantly elevated signals and 67 probe sets (approximately 56 genes) had significantly lower signals in both orbital tissues and in peripheral blood from patients with sarcoidosis. The transcription factors, interferon-response factor 1, interferon-response factor 2, and nuclear factor kappaB, were strongly implicated in the expression of messenger RNA upregulated in common in the 3 tissues. Conclusions and Relevance: Gene expression in sarcoidosis involving the orbit or lacrimal gland can be distinguished from gene expression patterns in control tissue and overlaps with many transcripts upregulated or downregulated in the peripheral blood of patients with sarcoidosis. These observations suggest that common pathogenic mechanisms contribute to sarcoidosis in different sites. The observations support the hypothesis that a pattern of gene expression profiles could provide diagnostic information in patients with sarcoidosis.

Rouhizadeh, M., Prud'Hommeaux, E., Roark, B., & Van Santen, J. (2013). Distributional semantic models for the evaluation of disordered language. *2013 Conference of the North American Chapter of the Association for Computational Linguistics: Human Language Technologies, NAACL HLT 2013*, pp. 709-714.

Atypical semantic and pragmatic expression is frequently reported in the language of children with autism. Although this atypicality often manifests itself in the use of unusual or unexpected words and phrases, the rate of use of such unexpected words is rarely directly measured or

quantified. In this paper, we use distributional semantic models to automatically identify unexpected words in narrative retellings by children with autism. The classification of unexpected words is sufficiently accurate to distinguish the retellings of children with autism from those with typical development. These techniques demonstrate the potential of applying automated language analysis techniques to clinically elicited language data for diagnostic purposes. © 2013 Association for Computational Linguistics.

Rozanov, D., Spellman, P., Savinov, A., & Strongin, A. Y. (2015). A humanized leucine zipper-TRAIL hybrid induces apoptosis of tumors both in vitro and in vivo. *PloS One*, *10*(4), e0122980.

Evidence suggests that stimulating apoptosis in malignant cells without inflicting collateral damage to the host's normal tissues is a promising cancer therapy. Chemo- and radiation therapies that, especially if combined, induce apoptosis in tumor cells have been used for treating cancer patients for decades. These treatments, however, are limited in their ability to discriminate between malignant and non-malignant cells and, therefore, produce substantial healthy tissue damage and subsequent toxic side-effects. In addition, as a result of these therapies, many tumor types acquire an apoptosis-resistant phenotype and become more aggressive and metastatic. Tumor necrosis factor-Related Apoptosis-Inducing Ligand (TRAIL) has been considered a promising and reliable selective inducer of apoptosis in cancerous cells. TRAIL, however, is not uniformly effective in cancer and multiple cancer cell types are considered resistant to natural TRAIL. To overcome this deficiency of TRAIL, we have earlier constructed a yeast-human hybrid leucine zipper-TRAIL in which the yeast GCN4-pII leucine zipper was fused to human TRAIL (GCN4-TRAIL). This construct exhibited a significantly improved anti-tumor apoptotic activity and safety, but is potentially immunogenic in humans. Here, we report a novel, potent, and fully human ATF7 leucine zipper-TRAIL (ATF7-TRAIL) fusion construct that is expected to have substantially lower immunogenicity. In solution, ATF7-TRAIL exists solely as a trimer with a  $T_m$  of 80 degrees C and is active against cancer cells both in vitro and in vivo, in a mouse tumor xenograft model. Our data suggest that our re-engineered TRAIL is a promising candidate for further evaluation as an antitumor agent.

Ruffell, B., & Coussens, L. M. (2015). Macrophages and therapeutic resistance in cancer. *Cancer Cell*, 27(4), 462-472.

How neoplastic cells respond to therapy is not solely dependent on the complexity of the genomic aberrations they harbor but is also regulated by numerous dynamic properties of the tumor microenvironment. Identifying and targeting critical pathways that improve therapeutic efficacy by bolstering anti-tumor immune responses holds great potential for improving outcomes and impacting long-term patient survival. Macrophages are key regulators of homeostatic tissue and tumor microenvironments. Therefore, therapeutics impacting macrophage presence and/or bioactivity have shown promise in preclinical models and are now being evaluated in the clinic. This review discusses the molecular/cellular pathways identified so far whereby macrophages mediate therapeutic responses.

Russell, P. K., Clarke, M. V., Cheong, K., Anderson, P. H., Morris, H. A., Wren, K. M., et al. (2015).

Androgen receptor action in osteoblasts in male mice is dependent on their stage of maturation. *Journal of Bone and Mineral Research*, 30(5), 809-823.

Androgen action via the androgen receptor (AR) is essential for normal skeletal growth and bone maintenance post-puberty in males; however, the molecular and cellular mechanisms by which androgens exert their actions in osteoblasts remains relatively unexplored in vivo. To identify autonomous AR actions in osteoblasts independent of AR signaling in other tissues, we compared the extent to which the bone phenotype of the Global-ARKO mouse was restored by replacing the AR in osteoblasts commencing at either the 1) proliferative or 2) mineralization stage of their maturation. In trabecular bone, androgens stimulated trabecular bone accrual during growth via the AR in proliferating osteoblasts and maintained trabecular bone post-puberty via the AR in mineralizing osteoblasts, with its predominant action being to inhibit bone resorption by decreasing the ratio of receptor activator of NF- $\kappa$ B ligand (RANKL) to osteoprotegerin (OPG) gene expression. During growth, replacement of the AR in proliferating but not mineralizing osteoblasts of Global-ARKOs was able to partially restore periosteal circumference, supporting the concept that androgen action in cortical bone to increase bone size during growth is mediated via the AR in proliferating osteoblasts. This study provides further significant insight into the mechanism of androgen action via the AR in osteoblasts, demonstrating that it is dependent on the stage of

osteoblast maturation. © 2014 American Society for Bone and Mineral Research. © 2014 American Society for Bone and Mineral Research.

Ryan, M., Weissman, J. L., & Kaylie, D. (2015). Is gadolinium contrast enhancement necessary in screening MRI for asymmetric sensorineural hearing loss? *Laryngoscope*, *125*(4), 783-784.

Saint-Martin, C., Zhou, Q., Martin, G. M., Vaury, C., Leroy, G., Arnoux, J. -, et al. (2015). Monoallelic ABCC8 mutations are a common cause of diazoxide-unresponsive diffuse form of congenital hyperinsulinism. *Clinical Genetics*, *87*(5), 448-454.

ABCC8 encodes a subunit of the  $\beta$ -cell potassium channel (KATP) whose loss of function is responsible for congenital hyperinsulinism (CHI). Patients with two recessive mutations of ABCC8 typically have severe diffuse forms of CHI unresponsive to diazoxide. Some dominant ABCC8 mutations are responsible for a subset of diffuse diazoxide-unresponsive forms of CHI. We report the analysis of 21 different ABCC8 mutations identified in 25 probands with diazoxide-unresponsive diffuse CHI and carrying a single mutation in ABCC8. Nine missense ABCC8 mutations were subjected to in vitro expression studies testing traffic efficiency and responses of mutant channels to activation by MgADP and diazoxide. Eight of the 9 missense mutations exhibited normal trafficking. Seven of the 8 mutants reaching the plasma membrane had dramatically reduced response to MgADP or to diazoxide (<10% of wild-type response). In our cohort, dominant KATP mutations account for 22% of the children with diffuse unresponsive-diazoxide CHI. Their clinical phenotype being indistinguishable from that of children with focal CHI and diffuse CHI forms due to two recessive KATP mutations, we show that functional testing is essential to make the most reliable diagnosis and offer appropriate genetic counseling. © 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Saitz, T. R., & Serefoglu, E. C. (2015). Men enjoy a year of significant progress. *Nature Reviews Urology*, *12*(2), 73-74.

Male sexual medicine has continued to evolve and several publications related to premature ejaculation, lower urinary tract symptoms, Peyronie's disease and testosterone replacement therapy have provided new insights in these fields. Our understanding has been revolutionized by

these studies and clinical management in male sexual dysfunction has improved. © 2015  
Macmillan Publishers Limited. All rights reserved.

Salter, M. L., Gupta, N., Massie, A. B., McAdams-DeMarco, M. A., Law, A. H., Jacob, R. L., et al.

(2015). Perceived frailty and measured frailty among adults undergoing hemodialysis: A cross-sectional analysis. *BMC Geriatrics*, 15(1), 52.

**BACKGROUND:** Frailty, a validated measure of physiologic reserve, predicts adverse health outcomes among adults with end-stage renal disease. Frailty typically is not measured clinically; instead, a surrogate-perceived frailty-is used to inform clinical decision-making. Because correlations between perceived and measured frailty remain unknown, the aim of this study was to assess their relationship. **METHODS:** 146 adults undergoing hemodialysis were recruited from a single dialysis center in Baltimore, Maryland. Patient characteristics associated with perceived (reported by nephrologists, nurse practitioners (NPs), or patients) or measured frailty (using the Fried criteria) were identified using ordered logistic regression. The relationship between perceived and measured frailty was assessed using percent agreement, kappa statistic, Pearson's correlation coefficient, and prevalence of misclassification of frailty. Patient characteristics associated with misclassification were determined using Fisher's exact tests, t-tests, or median tests. **RESULTS:** Older age (adjusted OR [aOR] = 1.36, 95%CI:1.11-1.68, P = 0.003 per 5-years older) and comorbidity (aOR = 1.49, 95%CI:1.27-1.75, P < 0.001 per additional comorbidity) were associated with greater likelihood of nephrologist-perceived frailty. Being non-African American was associated with greater likelihood of NP- (aOR = 5.51, 95%CI:3.21-9.48, P = 0.003) and patient- (aOR = 4.20, 95%CI:1.61-10.9, P = 0.003) perceived frailty. Percent agreement between perceived and measured frailty was poor (nephrologist, NP, and patient: 64.1%, 67.0%, and 55.5%). Among non-frail participants, 34.4%, 30.0%, and 31.6% were perceived as frail by a nephrologist, NP, or themselves. Older adults (P < 0.001) were more likely to be misclassified as frail by a nephrologist; women (P = 0.04) and non-African Americans (P = 0.02) were more likely to be misclassified by an NP. Neither age, sex, nor race was associated with patient misclassification. **CONCLUSIONS:** Perceived frailty is an inadequate proxy for measured frailty among patients undergoing hemodialysis.

Sambasivan, C. N., Underwood, S. J., Cho, S. D., Kiraly, L. N., Hamilton, G. J., Kofoed, J. T., et al.

(2010). Comparison of abdominal damage control surgery in combat versus civilian trauma. *The Journal of Trauma*, 69, S168-S174.

**BACKGROUND:** The majority of individuals who perform damage control surgery in the military arena are trained in civilian venues. Therefore, it is important to compare and contrast damage control performed in civilian and military settings. In contrast to civilian trauma, which is primarily caused by blunt injury and addressed at one or two surgical facilities, combat casualties primarily sustain explosion-related injuries and undergo treatment at multiple levels of care across continents. We aimed to compare patients undergoing abdominal damage control surgery across these two very different settings. **METHODS:** Parallel retrospective reviews were conducted over 2 years (2005-2006) in a combat setting and at a US Level I trauma center. Patients were examined during the first 7 days after injury. **RESULTS:** The civilian population (CP) was older (40 vs. 23;  $p < 0.01$ ) with a higher injury severity score (35 vs. 27;  $p < 0.02$ ). The CP experienced greater blunt injury than the military population (MP) (83 vs. 4%;  $p < 0.01$ ). Explosion-related injury was only present in the MP (64%). At baseline, the CP presented with lower systolic blood pressure (108 vs. 126) and larger base deficit (9.8 vs. 6.5;  $p < 0.05$ ). The MP underwent more surgeries (3.5 vs. 2.9;  $p = 0.02$ ) with similar rates of fascial closure (48.7% vs. 70.0%;  $p = 0.11$ ). Complication rates were similar between the CP and the MP (43% vs. 58%, respectively;  $p = 0.14$ ). **CONCLUSIONS:** Military and civilian trauma patients who undergo damage control surgery experience similar fascial closure rates despite differing demographics and widely disparate mechanisms of injury. The MP undergoes a greater number of procedures than the CP, but complication rates do not differ between the groups.

Sarracino, D. C., Tarantal, A. F., Lee, C. C. I., Martinez, M., Jin, X., Wang, X., et al. (2014). Effects of vector backbone and pseudotype on lentiviral vector-mediated gene transfer: Studies in infant ADA-deficient mice and rhesus monkeys. *Molecular Therapy*, 22(10), 1803-1816.

Systemic delivery of a lentiviral vector carrying a therapeutic gene represents a new treatment for monogenic disease. Previously, we have shown that transfer of the adenosine deaminase (ADA) cDNA in vivo rescues the lethal phenotype and reconstitutes immune function in ADA-deficient mice. In order to translate this approach to ADA-deficient severe combined immune

deficiency patients, neonatal ADA-deficient mice and newborn rhesus monkeys were treated with species-matched and mismatched vectors and pseudotypes. We compared gene delivery by the HIV-1-based vector to murine  $\gamma$ -retroviral vectors pseudotyped with vesicular stomatitis virus-glycoprotein or murine retroviral envelopes in ADA-deficient mice. The vesicular stomatitis virus-glycoprotein pseudotyped lentiviral vectors had the highest titer and resulted in the highest vector copy number in multiple tissues, particularly liver and lung. In monkeys, HIV-1 or simian immunodeficiency virus vectors resulted in similar biodistribution in most tissues including bone marrow, spleen, liver, and lung. Simian immunodeficiency virus pseudotyped with the gibbon ape leukemia virus envelope produced 10- to 30-fold lower titers than the vesicular stomatitis virus-glycoprotein pseudotype, but had a similar tissue biodistribution and similar copy number in blood cells. The relative copy numbers achieved in mice and monkeys were similar when adjusted to the administered dose per kg. These results suggest that this approach can be scaled-up to clinical levels for treatment of ADA-deficient severe combined immune deficiency subjects with suboptimal hematopoietic stem cell transplantation options. © The American Society of Gene & Cell Therapy.

Saugstad, J. A. (2015). Non-coding RNAs in stroke and neuroprotection. *Frontiers in Neurology*, 6, 50.

This review will focus on the current state of knowledge regarding non-coding RNAs (ncRNA) in stroke and neuroprotection. There will be a brief introduction to microRNAs (miRNA), long ncRNAs (lncRNA), and piwi-interacting RNAs (piRNA), followed by evidence for the regulation of ncRNAs in ischemia. This review will also discuss the effect of neuroprotection induced by a sublethal duration of ischemia or other stimuli given before a stroke (preconditioning) on miRNA expression and the role of miRNAs in preconditioning-induced neuroprotection. Experimental manipulation of miRNAs and/or their targets to induce pre- or post-stroke protection will also be presented, as well as discussion on miRNA responses to current post-stroke therapies. This review will conclude with a brief discussion of future directions for ncRNAs studies in stroke, such as new approaches to model complex ncRNA datasets, challenges in ncRNA studies, and the impact of extracellular RNAs on human diseases such as stroke.

Saultz, J. (2015). Income disparity and student career choice. *Family Medicine*, 47(3), 173-174.

Saultz, J. (2015). Out of practice. *Family Medicine*, 47(5), 341-342.

Saunders, G. H., Vachhani, J. J., Galvez, G., & Griest, S. E. (2015). Formative evaluation of a multimedia self-administered computerized hearing loss prevention program. *International Journal of Audiology*, 54(4), 234-240.

Objective: To determine which features make a computer-based hearing health education intervention effective, easy to use, and enjoyable. The study examined which features of a multimedia self-administered computerized hearing loss prevention program, developed by the National Center for Rehabilitative Auditory Research (referred to as the NCRAR-HLPP), users liked and disliked, and the reasons why. Design: A formative evaluation was conducted in which participants completed a questionnaire to assess knowledge and attitudes towards hearing and hearing loss prevention, used the NCRAR-HLPP, completed the questionnaire for a second time, and were interviewed to learn their opinions about the NCRAR-HLPP. Study sample: Twenty-five male and four female Veterans recruited from the Portland VA Medical Center who were aged between 25 and 65 years. Results: Participants reported that using the NCRAR-HLPP was a positive experience. Ease of use, multimedia content, personal relevance, and use of emotion were positive features of the program. The questionnaire showed increased knowledge and improved attitude scores following use of the program. Conclusion: This formative evaluation showed changes designed to target user preferences and improve user instructions will be made in future versions of the program. © 2014 British Society of Audiology, International Society of Audiology, and Nordic Audiological Society.

Sawyer, T., White, M., Zaveri, P., Chang, T., Ades, A., French, H., et al. (2015). Learn, see, practice, prove, do, maintain: An evidence-based pedagogical framework for procedural skill training in medicine. *Academic Medicine : Journal of the Association of American Medical Colleges*, Acquisition of competency in procedural skills is a fundamental goal of medical training. In this Perspective, the authors propose an evidence-based pedagogical framework for procedural skill training. The framework was developed based on a review of the literature using a critical synthesis approach and builds on earlier models of procedural skill training in medicine. The authors begin by describing the fundamentals of procedural skill development. Then, a six-step

pedagogical framework for procedural skills training is presented: Learn, See, Practice, Prove, Do, and Maintain. In this framework, procedural skill training begins with the learner acquiring requisite cognitive knowledge through didactic education (Learn) and observation of the procedure (See). The learner then progresses to the stage of psychomotor skill acquisition and is allowed to deliberately practice the procedure on a simulator (Practice). Simulation-based mastery learning is employed to allow the trainee to prove competency prior to performing the procedure on a patient (Prove). Once competency is demonstrated on a simulator, the trainee is allowed to perform the procedure on patients with direct supervision, until he or she can be entrusted to perform the procedure independently (Do). Maintenance of the skill is ensured through continued clinical practice, supplemented by simulation-based training as needed (Maintain). Evidence in support of each component of the framework is presented. Implementation of the proposed framework presents a paradigm shift in procedural skill training. However, the authors believe that adoption of the framework will improve procedural skill training and patient safety.

Schully, S. D., Carrick, D. M., Mechanic, L. E., Srivastava, S., Anderson, G. L., Baron, J. A., et al. (2015). Leveraging biospecimen resources for discovery or validation of markers for early cancer detection. *Journal of the National Cancer Institute*, 107(4), 10.1093/jnci/djv012. Print 2015 Apr. Validation of early detection cancer biomarkers has proven to be disappointing when initial promising claims have often not been reproducible in diagnostic samples or did not extend to prediagnostic samples. The previously reported lack of rigorous internal validity (systematic differences between compared groups) and external validity (lack of generalizability beyond compared groups) may be effectively addressed by utilizing blood specimens and data collected within well-conducted cohort studies. Cohort studies with prediagnostic specimens (eg, blood specimens collected prior to development of clinical symptoms) and clinical data have recently been used to assess the validity of some early detection biomarkers. With this background, the Division of Cancer Control and Population Sciences (DCCPS) and the Division of Cancer Prevention (DCP) of the National Cancer Institute (NCI) held a joint workshop in August 2013. The goal was to advance early detection cancer research by considering how the infrastructure of cohort studies that already exist or are being developed might be leveraged to include

appropriate blood specimens, including prediagnostic specimens, ideally collected at periodic intervals, along with clinical data about symptom status and cancer diagnosis. Three overarching recommendations emerged from the discussions: 1) facilitate sharing of existing specimens and data, 2) encourage collaboration among scientists developing biomarkers and those conducting observational cohort studies or managing healthcare systems with cohorts followed over time, and 3) conduct pilot projects that identify and address key logistic and feasibility issues regarding how appropriate specimens and clinical data might be collected at reasonable effort and cost within existing or future cohorts.

Scott Schwoerer, J., Cooper, G., & Van Calcar, S. (2015). Rhabdomyolysis in a neonate due to very long chain acyl CoA dehydrogenase deficiency. *Molecular Genetics and Metabolism Reports*, 3, 39-41.

Very long chain acyl CoA dehydrogenase deficiency (VLCADD) is an inborn error in long chain fatty acid oxidation with significant variability in the severity and timing of its clinical presentation. Neonatal presentations of VLCADD have included hypoglycemia and cardiomyopathy while rhabdomyolysis is usually a later onset complication. We describe a neonate with VLCADD presenting with rhabdomyolysis prior to the return of an abnormal newborn screen. This report suggests that evaluating for rhabdomyolysis, in addition to a cardiac and hepatic work-up, is an important part of the initial evaluation of an infant with an abnormal newborn screen suggesting a diagnosis of VLCADD. © 2015 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license.

Sedgley, C. M., & Jacinto, R. C. (2014). *Biofilms in root canal infections* Wiley Blackwell.

This chapter describes the general characteristics of biofilms and analyzes biofilms associated with root canal (RC) infections. Microbial cells occupy only a small portion of the biofilm. The majority of the biofilm structure is a highly heterogeneous matrix composed of extracellular polymeric substances (EPS) produced by cells within the biofilm. The distance between microorganisms and their spatial distribution within biofilms are critical factors for intermicrobial communication processes in biofilms. In the ever-changing biofilm environment, microbial cells encounter a multitude of stresses and challenges. These include exposure to nutrient limitation,

reactive oxygen and nitrogen species, membrane damage, and elevated temperature. Infected RCs harbor a multispecies population of facultative and strict anaerobic gram-positive and gram-negative bacteria, spirochetes, yeasts, archaea, and other unidentified species. Several in-vitro models have been used to study biofilms of relevance to RC treatment. These studies typically focus on the efficacy of antimicrobial agents against single- or multispecies biofilms. © 2014 by John Wiley & Sons, Inc. All rights reserved.

Selph, S. S., Ginsburg, A. D., & Chou, R. (2014). Impact of contacting study authors to obtain additional data for systematic reviews: Diagnostic accuracy studies for hepatic fibrosis.

*Systematic Reviews*, 3(1)

Background: Seventeen of 172 included studies in a recent systematic review of blood tests for hepatic fibrosis or cirrhosis reported diagnostic accuracy results discordant from  $2 \times 2$  tables, and 60 studies reported inadequate data to construct  $2 \times 2$  tables. This study explores the yield of contacting authors of diagnostic accuracy studies and impact on the systematic review findings. Methods: Sixty-six corresponding authors were sent letters requesting additional information or clarification of data from 77 studies. Data received from the authors were synthesized with data included in the previous review, and diagnostic accuracy sensitivities, specificities, and positive and likelihood ratios were recalculated. Results: Of the 66 authors, 68% were successfully contacted and 42% provided additional data for 29 out of 77 studies (38%). All authors who provided data at all did so by the third emailed request (ten authors provided data after one request). Authors of more recent studies were more likely to be located and provide data compared to authors of older studies. The effects of requests for additional data on the conclusions regarding the utility of blood tests to identify patients with clinically significant fibrosis or cirrhosis were generally small for ten out of 12 tests. Additional data resulted in reclassification (using median likelihood ratio estimates) from less useful to moderately useful or vice versa for the remaining two blood tests and enabled the calculation of an estimate for a third blood test for which previously the data had been insufficient to do so. We did not identify a clear pattern for the directional impact of additional data on estimates of diagnostic accuracy. Conclusions: We successfully contacted and received results from 42% of authors who provided data for 38% of included studies. Contacting authors of studies evaluating the diagnostic

accuracy of serum biomarkers for hepatic fibrosis and cirrhosis in hepatitis C patients impacted conclusions regarding diagnostic utility for two blood tests and enabled the calculation of an estimate for a third blood test. Despite relatively extensive efforts, we were unable to obtain data to resolve discrepancies or complete  $2 \times 2$  tables for 62% of studies. © 2014 Selph et al.

Serota, D. P., Halvorson, S., & Desai, S. (2015). A couple's colitis. *Journal of General Internal Medicine,*

Sheridan, D. C., Spiro, D. M., Fu, R., Johnson, K. P., Sheridan, J. S., Oue, A. A., et al. (2015). Mental health utilization in a pediatric emergency department. *Pediatric Emergency Care,*

OBJECTIVE: Mental health complaints are frequent in the pediatric emergency department (PED). The objective of this study was to describe trends over time in PED utilization for mental health care at in a single pediatric tertiary care hospital. It is our hypothesis that the resources used by this patient population are high and that mental health-related visits have increased over the most recent decade. METHODS: This was a retrospective study of all pediatric mental health presentations to the PED from January 2009 to July 2013 at a single pediatric hospital. All patients aged 1 to 19 years with an International Classification of Diseases, Ninth Revision code of 291, 292, 295 to 309, and 311 to 314 were included. Data collected included demographic data, medications received, restraint use, suicidality, length of stay (LOS), charges incurred, final disposition, and daily PED operation variables. Trends over time in presentation, charges, and LOS were analyzed using multiple mixed effects regression models after adjusting for potential patient and PED level confounding variables and clustering of multiple visits within patients.

RESULTS: A total of 732 PED visits from 2009 to 2013 were identified representing 646 unique patients. The average age was 13.8 years, and 53% were male. Approximately 25% of the patients expressed suicidal ideation, and 44% of those had attempted suicide before arrival. Behavioral or chemical restraints were used in 33% of patients during their PED visit. There were statistically significant increases in annual visits, LOS, and charges over this period ( $P < 0.05$ ). Increased charges were significantly associated with longer LOS ( $P = 0.0062$ ). Charges ( $P = 0.46$ ) and LOS ( $P = 0.62$ ) were not significantly different between suicidal and nonsuicidal patients. Approximately 21% of patients were admitted or transferred to another facility.

CONCLUSIONS: In this single-center study, we found evidence that the resources required to care for pediatric patients with mental health complaints have increased significantly over time both by increased number of annual visits and an increasing LOS. Further research is necessary to determine if our data are consistent with national trends to further our understanding of the problem and improve resource allocation.

Shi, Z., & Brooks, V. L. (2015). Leptin differentially increases sympathetic nerve activity and its baroreflex regulation in female rats: Role of oestrogen. *Journal of Physiology*, 593(7), 1633-1647.

Obesity and hypertension are commonly associated, and activation of the sympathetic nervous system is considered to be a major contributor, at least in part due to the central actions of leptin. However, while leptin increases sympathetic nerve activity (SNA) in males, whether leptin is equally effective in females is unknown. Here, we show that intracerebroventricular (i.c.v.) leptin increases lumbar (LSNA) and renal (RSNA) SNA and baroreflex control of LSNA and RSNA in  $\alpha$ -chloralose anaesthetized female rats, but only during pro-oestrus. In contrast, i.c.v. leptin increased basal and baroreflex control of splanchnic SNA (SSNA) and heart rate (HR) in rats in both the pro-oestrus and dioestrus states. The effects of leptin on basal LSNA, RSNA, SSNA and HR were similar in males and pro-oestrus females; however, i.c.v. leptin increased mean arterial pressure (MAP) only in males. Leptin did not alter LSNA or HR in ovariectomized rats, but its effects were normalized with 4 days of oestrogen treatment. Bilateral nanoinjection of SHU9119 into the paraventricular nucleus of the hypothalamus (PVN), to block  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH) type 3 and 4 receptors, decreased LSNA in leptin-treated pro-oestrus but not dioestrus rats. Unlike leptin, i.c.v. insulin infusion increased basal and baroreflex control of LSNA and HR similarly in pro-oestrus and dioestrus rats; these responses did not differ from those in male rats. We conclude that, in female rats, leptin's stimulatory effects on SNA are differentially enhanced by oestrogen, at least in part via an increase in  $\alpha$ -MSH activity in the PVN. These data further suggest that the actions of leptin and insulin to increase the activity of various sympathetic nerves occur via different neuronal pathways or cellular mechanisms. These results may explain the poor correlation in females of SNA with adiposity, or of MAP with leptin. © 2015 The Physiological Society.

Shi, Z., Fan, D., Johnson, R. L., Tratnyek, P. G., Nurmi, J. T., Wu, Y., et al. (2015). Methods for characterizing the fate and effects of nano zerovalent iron during groundwater remediation. *Journal of Contaminant Hydrology*,

The emplacement of nano zerovalent iron (nZVI) for groundwater remediation is usually monitored by common measurements such as pH, total iron content, and oxidation-reduction potential (ORP) by potentiometry. However, the interpretation of such measurements can be misleading because of the complex interactions between the target materials (e.g., suspensions of highly reactive and variably aggregated nanoparticles) and aquifer materials (sediments and groundwater), and multiple complications related to sampling and detection methods. This paper reviews current practice for both direct and indirect characterizations of nZVI during groundwater remediation and explores prospects for improving these methods and/or refining the interpretation of these measurements. To support our recommendations, results are presented based on laboratory batch and column studies of nZVI detection using chemical, electrochemical, and geophysical methods. Chemical redox probes appear to be a promising new method for specifically detecting nZVI, based on laboratory tests. The potentiometric and voltammetric detections of iron nanoparticles, using traditional stationary disc electrodes, rotating disc electrodes, and flow-through cell disc electrodes, provide insight for interpreting ORP measurements, which are affected by solution chemistry conditions and the interactions between iron nanoparticles and the electrode surface. The geophysical methods used for characterizing ZVI during groundwater remediation are reviewed and its application for nZVI detection is assessed with results of laboratory column experiments.

Siciliano, C. A., Calipari, E. S., Cuzon Carlson, V. C., Helms, C. M., Lovinger, D. M., Grant, K. A., et al. (2015). Voluntary ethanol intake predicts kappa-opioid receptor supersensitivity and regionally distinct dopaminergic adaptations in macaques. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 35(15), 5959-5968.

The dopaminergic projections from the ventral midbrain to the striatum have long been implicated in mediating motivated behaviors and addiction. Previously it was demonstrated that kappa-opioid receptor (KOR) signaling in the striatum plays a critical role in the increased reinforcing efficacy of ethanol following ethanol vapor exposure in rodent models. Although

rodents have been used extensively to determine the neurochemical consequences of chronic ethanol exposure, establishing high levels of voluntary drinking in these models has proven difficult. Conversely, nonhuman primates exhibit similar intake and pattern to humans in regard to drinking. Here we examine the effects of chronic voluntary ethanol self-administration on dopamine neurotransmission and the ability of KORs to regulate dopamine release in the dorsolateral caudate (DLC) and nucleus accumbens (NAc) core. Using voltammetry in brain slices from cynomolgus macaques after 6 months of ad libitum ethanol drinking, we found increased KOR sensitivity in both the DLC and NAc. The magnitude of ethanol intake predicted increases in KOR sensitivity in the NAc core, but not the DLC. Additionally, ethanol drinking increased dopamine release and uptake in the NAc, but decreased both of these measures in the DLC. These data suggest that chronic daily drinking may result in regionally distinct disruptions of striatal outputs. In concert with previous reports showing increased KOR regulation of drinking behaviors induced by ethanol exposure, the strong relationship between KOR activity and voluntary ethanol intake observed here gives further support to the hypothesis that KORs may provide a promising pharmacotherapeutic target in the treatment of alcoholism.

Simon, J. H., & Wolinsky, J. S. (2011). *Measures of acute and chronic lesions visualized by conventional magnetic resonance imaging* Cambridge University Press.

Introduction Magnetic resonance imaging (MRI) plays an essential role in the diagnosis of multiple sclerosis (MS), is useful as a prognostic aid, has been accepted as a primary outcome measure in exploratory trials of the development of new drugs for disease modification, is an essential supportive secondary outcome variable for drug registration, and is invaluable in the management of individual patients. This chapter will review the use of conventional MRI (cMRI) as generally available to the practitioner, touch on newer MR-based tools as they illuminate our understanding of MS pathology as defined by cMRI, and explore the justification of the use of cMRI in these settings. One of the most profound changes in our modern conceptualization of MS pathogenesis arises from MRI. Serial imaging enabled recognition of how dynamic the changes are that underlie the evolution of lesions in MS patients in the absence of those clinical events that characterize relapsing and, to a lesser extent, progressive forms of the disease. This has led to a model of how lesions evolve over time that as a first approximation characterizes most of the

evolving pathology of MS for many but not all patients, and for most but not all developing MRI-defined lesions. MRI-defined lesion evolution largely stems from observation of changes in the white matter expanses of the cerebral hemispheres, brain stem, and spinal cord. However, there are some differences in the signatures of these lesions as they occur in different brain topographies. Somewhat more elusive is the evolution of intracortical lesions in MS (Chapter 13).  
© Cambridge University Press 2011.

Simon-Dack, S. L., Holtgraves, T., Hernandez, K., & Thomas, C. (2015). Resting EEG and behavioural correlates of interhemispheric transfer times. *Laterality*, Correlations between the relative speeds of left-to-right and right-to-left interhemispheric transfer times and resting quantitative electroencephalography activity were examined in order to determine if variability in interhemispheric transfer was related to individual variability in resting neural firing patterns. Resting electroencephalograph frequencies for 32 participants were regressed for 4 frequency bands at 8 different locations calculated for asymmetrical activation through subtracting the left from right average spectral power of each. Participants also completed a series of behavioural tasks that are typically localized to the right hemisphere (RH). Results indicate that the frontal medial average spectral power of the beta band is correlated with the speed of transfer such that larger resting beta values in the right as compared to left location are associated with faster right-to-left interhemispheric transfer times and that larger resting beta values in the left as compared to right location are associated with faster left-to-right interhemispheric transfer times. Furthermore, enhanced performance on tasks typically localized to the RH is correlated with slower right-to-left interhemispheric transfer times, suggesting that the dominance of one hemisphere may come at a cost to interhemispheric communication. © 2015 Taylor & Francis

Slatore, C. G., Golden, S. E., Ganzini, L., Wiener, R. S., & Au, D. H. (2015). Distress and patient-centered communication among veterans with incidental (not screen-detected) pulmonary nodules: A cohort study. *Annals of the American Thoracic Society*, 12(2), 184-192.  
Rationale: Incidental pulmonary nodule detection is postulated to cause distress, but the frequency and magnitude of that distress have not been reported. The quality of patient-clinician

communication and the perceived risk of lung cancer may influence distress Objectives: To evaluate the association of communication processes with distress and the perceived risk of lung cancer using validated instruments. Methods: We conducted a prospective cohort study of patients with incidentally detected nodules who received care at one Department of Veterans Affairs Medical Center. We measured distress with the Impact of Event Scale and patient-centered communication with the Consultation Care Measure, both validated instruments. Risk of lung cancer was self-reported by participants. We used multivariable adjusted logistic regression to measure the association of communication quality with distress. Measurements and Main Results: Among 122 Veterans with incidental nodules, 23%, 12%, and 4% reported experiencing mild, moderate, and severe distress, respectively, at the time they were informed of the pulmonary nodule. Participant-reported risk of lung cancer was not associated with distress. In the adjusted model, high-quality communication was associated with decreased distress (odds ratio [OR] = 0.28, 95% confidence interval [CI] = 0.08-1.00, P = 0.05). Among participants who reported a risk of malignancy of 30% or less, high-quality communication was associated with decreased distress (OR = 0.15, 95% CI = 0.02-0.92, P = 0.04), but was not associated with distress for those who reported a risk greater than 30% (OR = 0.12 (95% CI = 0.00-3.97, P = 0.24), although the P value for interaction was not significant. Conclusions: Veterans with incidental pulmonary nodules frequently reported inadequate information exchange regarding their nodule. Many patients experience distress after they are informed that they have a pulmonary nodule, and high-quality patient-clinician communication is associated with decreased distress. Communication strategies that only target improved knowledge of the risk of malignancy may not be sufficient to reduce the distress associated with nodule detection. Copyright © 2015 by the American Thoracic Society.

Sonnenberg, A. (2015). Adverse outcomes: Why bad things happen to good people. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, 13(5), 820-823.e1.

Sonnenberg, A. (2015). Modeling lengthy work-ups in gastrointestinal bleeding. *Clinical Gastroenterology and Hepatology*, 13(3), 433-439.

Multiple procedures and medical devices are being used in a complex interplay to diagnose and treat gastrointestinal bleeding. The aim of the study was to develop a mathematical model that helps in estimating the average number of procedures to be expected in the general management of gastrointestinal bleeding. The modeling process serves as an example of how mathematical analysis in general can be used to answer unresolved clinical questions, lead to a better understanding of the underlying influences in a disease process, and provide a starting point for future clinical trials. The analysis uses a Markov chain to model the transition probabilities among consecutive interventions used to find and treat a bleeding site. The results show that starting a work-up of gastrointestinal bleeding with an esophagogastroduodenoscopy will lead on average to 2.69 procedures per patient. Of these expected procedures, 1.46 will be esophagogastroduodenoscopies, 0.69 colonoscopies, 0.25 video capsule endoscopies, 0.14 double-balloon enteroscopies, and 0.14 procedures from interventional radiology. Management chains initiated with a colonoscopy result in similar outcomes. Among 10,000 simulated individual patients, the number of procedures varies between 1 and 16 consecutive procedures, with 95% of all patients undergoing 6 procedures or less. The outcomes of the model suggest that the published success rates of endoscopic and radiographic procedures are overly optimistic. The results also point to the need to generate clinical data through future studies that more reliably account for treatment failures and the interchange among various complementary diagnostic modalities. © 2015 AGA Institute.

Soto, P. L., Grandy, D. K., Hursh, S. R., & Katz, J. L. (2015). Erratum to: Behavioral economics of food reinforcement and the effects of prefeeding, extinction, and eticlopride in dopamine D2 receptor mutant mice. *Psychopharmacology*,

Souza, P. E., Wright, R. A., Blackburn, M. C., Tatman, R., & Gallun, F. J. (2015). Individual sensitivity to spectral and temporal cues in listeners with hearing impairment. *Journal of Speech, Language, and Hearing Research*, 58(2), 520-534.

Purpose: The present study was designed to evaluate use of spectral and temporal cues under conditions in which both types of cues were available. Method: Participants included adults with normal hearing and hearing loss. We focused on 3 categories of speech cues: static spectral

(spectral shape), dynamic spectral (formant change), and temporal (amplitude envelope). Spectral and/or temporal dimensions of synthetic speech were systematically manipulated along a continuum, and recognition was measured using the manipulated stimuli. Level was controlled to ensure cue audibility. Discriminant function analysis was used to determine to what degree spectral and temporal information contributed to the identification of each stimulus. Results: Listeners with normal hearing were influenced to a greater extent by spectral cues for all stimuli. Listeners with hearing impairment generally utilized spectral cues when the information was static (spectral shape) but used temporal cues when the information was dynamic (formant transition). The relative use of spectral and temporal dimensions varied among individuals, especially among listeners with hearing loss. Conclusion: Information about spectral and temporal cue use may aid in identifying listeners who rely to a greater extent on particular acoustic cues and applying that information toward therapeutic interventions. © 2015 American Speech-Language-Hearing Association.

Spencer, P. S., Palmer, V. S., & Mazumder, R. (2015). Probable toxic cause for suspected lychee-linked viral encephalitis. *Emerging Infectious Diseases*, 21(5), 904-905.

Speroff, L. (2008). Foreword. *Operative Obstetrics, Second Edition*, 9780521862486, xi-xii.

THE PROCESS OF EVOLUTION affects not only the characteristics of a species but also the adaptive technology between a species and its environment. The practice of obstetrics is devoted to maximizing the ability of each human being to confront the environment and to be part of the creative, modulating path of evolution. It is almost, if not totally, impossible to discern evolutionary human changes within our own lifetimes; however, it is a different story with the technology of our interactions. Obstetrics has changed, and it has changed rapidly. If the earth's lifetime were compressed into a single 24-hour day, humans would have appeared only 30 seconds ago. I cannot imagine what nanocalculation would be required to measure the history of operative obstetrics, yet that incredibly short measure of geologic time is packed with a geometrically increasing collection of events and stories. The interesting and comprehensive chapter on the history of operative delivery alone is worth the price of this book. Every contemporary obstetrician should know and learn from the history of obstetrics. Some might

argue that this history is truly the past, and that operative obstetrics today is a matter of a few simple choices. Even that judgment, however, must be based on a critical analysis of the operative choices. Only then can the individual obstetrician understand the reasons behind modern decisions. The modern focus on "evidence-based medicine" all too often fails to recognize the broad base of knowledge that is the foundation of clinical decision making. © John P. O'Grady 2008 and Cambridge University Press, 2009.

Srivatsal, S., Cholerton, B., Leverenz, J. B., Wszolek, Z. K., Uitti, R. J., Dickson, D. W., et al. (2015).

Cognitive profile of LRRK2-related parkinson's disease. *Movement Disorders*, 30(5), 728-733.

Background: Increasing evidence suggests that genetic factors play a role in the variability associated with cognitive performance in Parkinson's disease (PD). Mutations in the LRRK2 gene are the most common cause of monogenic PD; however, the cognitive profile of LRRK2-related PD is not well-characterized. Methods: A cohort of 1,447 PD patients enrolled in the PD Cognitive Genetics Consortium was screened for LRRK2 mutations and completed detailed cognitive testing. Associations between mutation carrier status and cognitive test scores were assessed using linear regression models. Results: LRRK2 mutation carriers (n=29) demonstrated better performance on the Mini Mental State Examination (P=0.03) and the Letter-Number Sequencing Test (P=0.005). A smaller proportion of LRRK2 carriers were demented (P=0.03). Conclusions: Our cross-sectional study demonstrates better performance on certain cognitive tests, as well as lower rates of dementia in LRRK2-related PD. Future longitudinal studies are needed to determine whether LRRK2 mutation carriers exhibit slower cognitive decline. © 2015 International Parkinson and Movement Disorder Society.

Stagg, S. M., Noble, A. J., Spilman, M., & Chapman, M. (2014). ResLog plots: A new metric for the quality of cryo-EM reconstructions. *Microscopy and Microanalysis*, 20(3), 1254-1255.

Su, E. J. (2005). *Pain management* Cambridge University Press.

Scope of the problem Acute pain is the most common complaint of patients presenting to the emergency department (ED), comprising 60% of presenting complaints in one study. Recognition and acknowledgment of a patient's pain, adequate treatment, and timely reassessment are essential to acute pain management in the ED. Unfortunately, it has been demonstrated that

many physicians fail to treat pain promptly or adequately in both inpatient and outpatient settings. Pain is whatever the experiencing person says it is, existing whenever he or she says it does. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage," "always subjective," and "learned through experiences related to injury in early life." Pain includes behavioral and physical indicators, in addition to self-report. Thus, preverbal, nonverbal, or cognitively-impaired individuals who experience pain can benefit from objective pain assessment. Fear and anxiety increase the perception of physical pain – the unfamiliar and frequently unfriendly ED environment does little to ameliorate a patient's pain. Acute pain is a symptom of injury or illness, which serves the biologic purpose of warning an individual of a problem and limiting activities that might exacerbate it. Acute pain is usually associated with identifiable pathology and causes anxiety. By convention, it is present for less than 6 months. Chronic, malignant pain is associated with a terminal disease, such as cancer or acquired immune deficiency syndrome (AIDS). © Cambridge University Press 2005 and Cambridge University Press, 2009.

Su, E. J. (2008). *Pharmacology of commonly utilized analgesic agents* Cambridge University Press.

**SCOPE OF THE PROBLEM** Emergency physicians must recognize and treat pain from many causes, from shingles to severe trauma, myocardial infarction to ureterolithiasis. Pain management is an important skill in emergency medicine, requiring recognition and acknowledgment of the patient's pain, adequate treatment, and prompt reevaluation. Analgesia is the "loss of sensitivity to pain," or the reduction of pain through therapy. The therapy is not solely pharmacologic in nature: psychological and social support as well as physical positioning for maximum comfort, all help to reduce a patient's perceived pain. Simply reassuring the patient that the provider is aware of the patient's pain and is actively working to relieve the pain can be as important as any medications used.

**CLINICAL ASSESSMENT** Approach to the Patient/Situation It is imperative for physicians to detect and measure pain rapidly so that they can begin treatment promptly and assess its effect. To the physician, the patient may not appear to be in pain, but he or she may actually be in severe pain. Careful listening, observation, and repeated solicitation may be necessary to fully elicit an admission of pain. Assessment must be both

qualitative (is pain present?) and quantitative (how much does it hurt? Has it improved with treatment?). Early reassessment must follow any treatments to ensure that it was adequate and without adverse effects, and that repeated doses are given promptly if needed. © John H. Burton and James Miner 2008 and Cambridge University Press, 2009.

Su, E. J. (2008). *Pharmacology of commonly utilized sedative agents* Cambridge University Press.

SCOPE OF THE PROBLEM A patient in pain and contemplating a procedure that will sharply increase the pain, even transiently, is understandably anxious. Anxiolysis, amnesia of a painful event, a decrease in spontaneous movement, and voluntary muscle relaxation increase the likelihood of success of a painful procedure and are the desired results of procedural sedation.

CLINICAL ASSESSMENT: APPROACH TO THE PATIENT/SITUATION Patients often wait too long for their pain to be treated. Untreated pain will increase a patient's anxiety and may result in the need for higher doses of both analgesics and sedatives. Each patient should be treated

individually and assessed according to his or her individual tolerance for pain and anxiety. Factors within the ED, such as volume, acuity, and staffing will also impact the decision about depth of sedation and which agents to use (Table 25-1). PAIN/SEDATION MANAGEMENT Safety, speed of onset, and ease of administration are the key elements affecting the choice of agents used for sedation in the ED. The agent and route of administration must ensure rapid onset of adequate analgesia and sedation; IV and inhalational routes ensure the fastest onset of action. Sometimes, establishing an IV can be extremely difficult, especially in toddlers or in chronically ill patients whose veins are friable. Transmucosally absorbed drugs (e.g., intranasal administration of ketamine, midazolam, or sufentanil) may provide enough pain relief that the patient can cooperate better with the IV start (Table 25-2). Pharmacologic Therapy Benzodiazepines Benzodiazepines are excellent sedative agents but have no analgesic effects. © John H. Burton and James Miner 2008 and Cambridge University Press, 2009.

Swartz, C. M. (2009). *Electroconvulsive and neuromodulation therapies* Cambridge University Press.

Electroconvulsive therapy (ECT) is a psychiatric treatment involving the induction of a seizure through the transmission of electricity into the brain. In the early eighties, ECT was replaced by far more effective psychopharmacologic medications as a primary treatment modality. Much of

the decline in use of ECT at that time was also ascribable to the number of complications associated with the technique. Because of recent refinements and a far better understanding of the scientific mechanisms underpinning ECT, this treatment modality has lately seen a resurgence in use in clinical practice. This book is the new definitive reference on electroconvulsive and neuromodulation therapy. It comprehensively covers both the scientific basis and clinical practice of ECT, as well as providing readers with administrative perspectives for the training and management of this modality in clinical practice. The newer forms of non-convulsive electrical and magnetic brain stimulation therapy are also covered in detail and presented as a separate section. . © Cambridge University Press 2009.

Swartz, C. M. (2009). Preface. *Electroconvulsive and Neuromodulation Therapies*, 9780521883887, xvii-xxx.

This book is dedicated to describing how electroconvulsive therapy (ECT) treats mental illness. Besides treating mental illness, ECT can prevent mental illness in several ways. First, ECT interrupts psychosis and catatonia and thereby prevents episodes of these from persisting and becoming chronic. Genetic data have identified similarities rather than distinctions between psychotic mood disorders and schizophrenia (e.g., Kishimoto et al., 2008; Taylor, 1992). These data complement epidemiologic–phenomenological studies that find continuous variation between psychotic mood disorders and schizophrenia, without a point of rarity to demarcate them. In other words, there is no known difference between schizophrenia and a psychotic (or catatonic) episode that has persisted. We should make every effort to interrupt these episodes before they become entrenched. In this way, ECT should prevent chronic schizophrenia. Second, but just as important, ECT circumvents using antipsychotic drugs in patients who would otherwise receive them. As detailed in Chapter 23, “Electroconvulsive therapy or antipsychotic drugs (or benzodiazepines for catatonia),” these medications can cause a variety of serious psychiatric, neurological, and medical impairments. It takes a powerful lot of faith to believe that patients with psychosis who receive antipsychotic medications will indeed achieve remission and then maintain it after these medications are stopped. In reality, the data show the opposite. Virtually 100% of patients started on antipsychotic medications for psychosis eventually receive the

diagnosis of schizophrenia on follow-up. Psychiatric diagnosis is simply not this reliable. © Cambridge University Press 2009.

Tarlock, K., Chang, B., Cooper, T., Gross, T., Gupta, S., Neudorf, S., et al. (2015). Sorafenib treatment following hematopoietic stem cell transplant in pediatric FLT3/ITD acute myeloid leukemia. *Pediatric Blood and Cancer*, 62(6), 1048-1054.

Background: FLT3/ITD is associated with poor outcomes in adult and pediatric acute myeloid leukemia (AML). Allogeneic hematopoietic stem cell transplantation (HSCT) can improve cure rates, however relapse is still common. Recent studies demonstrate the activity of FLT3 inhibitors, including sorafenib, in targeting the underlying mutation. Procedure: We conducted a retrospective study of 15 pediatric patients with FLT3/ITD+ AML treated with sorafenib within 18 months after receiving HSCT. Sorafenib was administered either as prophylaxis in patients considered at very high risk for relapse (n=6) or at the time of disease recurrence (n=9).

Results: Sorafenib was initiated at a median of 100 days post HSCT. Overall, 11/15 (73%) of patients experienced medically significant toxicities. Among patients who experienced toxicity, 6/11 (55%) received treatment at doses above what was later determined to be the maximum tolerated dose of sorafenib for pediatric leukemia. Importantly, sorafenib did not appear to exacerbate graft versus host disease. Our findings suggest that sorafenib may be of particular efficacy in patients with minimal residual disease (MRD); all patients who received sorafenib for MRD immediately prior to transplant or with emergence post-HSCT are alive and remain in complete remission at a median of 48 months post HSCT. Conclusions: Our case series suggests that sorafenib administration is feasible and tolerable in pediatric FLT3/ITD+ AML patients early post HSCT. Ongoing prospective controlled studies are needed to further define the dosing of sorafenib in the post-HSCT period and to determine the optimal context for this treatment approach. © 2015 Wiley Periodicals, Inc.

Tebo, B. M., Davis, R. E., Anitori, R. P., Connell, L. B., Schiffman, P., & Staudigel, H. (2015). Microbial communities in dark oligotrophic volcanic ice cave ecosystems of mt. erebus, antarctica. *Frontiers in Microbiology*, 6, 179.

The Earth's crust hosts a subsurface, dark, and oligotrophic biosphere that is poorly understood

in terms of the energy supporting its biomass production and impact on food webs at the Earth's surface. Dark oligotrophic volcanic ecosystems (DOVEs) are good environments for investigations of life in the absence of sunlight as they are poor in organics, rich in chemical reactants and well known for chemical exchange with Earth's surface systems. Ice caves near the summit of Mt. Erebus (Antarctica) offer DOVEs in a polar alpine environment that is starved in organics and with oxygenated hydrothermal circulation in highly reducing host rock. We surveyed the microbial communities using PCR, cloning, sequencing and analysis of the small subunit (16S) ribosomal and Ribulose-1,5-bisphosphate Carboxylase/Oxygenase (RubisCO) genes in sediment samples from three different caves, two that are completely dark and one that receives snow-filtered sunlight seasonally. The microbial communities in all three caves are composed primarily of Bacteria and fungi; Archaea were not detected. The bacterial communities from these ice caves display low phylogenetic diversity, but with a remarkable diversity of RubisCO genes including new deeply branching Form I clades, implicating the Calvin-Benson-Bassham (CBB) cycle as a pathway of CO<sub>2</sub> fixation. The microbial communities in one of the dark caves, Warren Cave, which has a remarkably low phylogenetic diversity, were analyzed in more detail to gain a possible perspective on the energetic basis of the microbial ecosystem in the cave. Atmospheric carbon (CO<sub>2</sub> and CO), including from volcanic emissions, likely supplies carbon and/or some of the energy requirements of chemoautotrophic microbial communities in Warren Cave and probably other Mt. Erebus ice caves. Our work casts a first glimpse at Mt. Erebus ice caves as natural laboratories for exploring carbon, energy and nutrient sources in the subsurface biosphere and the nutritional limits on life.

Terao, K., Kanenaga, R., Yoshida, T., Mizuno, K., & Bächinger, H. P. (2015). Temperature induced complex formation-deformation behavior of collagen model peptides and polyelectrolytes in aqueous solution. *Polymer (United Kingdom)*, *64*, 8-13.

Since the triple-helical collagen model peptides with a free N-terminus have three cationic groups at one end, it may have strong interactions with polyelectrolytes. In this study, complex formation behavior was investigated for sodium carboxymethyl amylose (NaCMA) + H-(Pro-Pro-Gly)<sub>10</sub>-OH (PPG<sub>10</sub>), a collagen model peptide, in aqueous NaCl with ionic strength of 10 mM and 100 mM by means of small-angle X-ray scattering (SAXS) and circular dichroism at different

temperatures. The previously reported [Macromolecules 2012, 45, 392-400] sodium polyacrylate (NaPAA) and H-(Gly-Pro-4-(R)-Hyp)<sup>9</sup>-OH (GPO9) system was also investigated to elucidate complex formation nearby the transition temperature region between triple helix and single coil of the peptide. The complex formed near the melting temperature of the triple helices, confirmed that the triple helical structure is directly related to the complex formation. © 2015 Elsevier Ltd. All rights reserved.

Tereshchenko, L. G., Waks, J. W., Kabir, M., Ghafoori, E., Shvilkin, A., & Josephson, M. E. (2015).

Analysis of speed, curvature, planarity and frequency characteristics of heart vector movement to evaluate the electrophysiological substrate associated with ventricular tachycardia. *Computers in Biology and Medicine*,

BACKGROUND: We developed a novel method of assessing ventricular conduction using the surface ECG. METHODS: Orthogonal ECGs of 81 healthy controls (age 39.0±14.2 y; 51.8% males; 94% white), were compared with iDower-transformed 12-lead ECGs (both 1000Hz), recorded in 8 patients with infarct-cardiomyopathy and sustained monomorphic ventricular tachycardia (VT) (age 68.0±7.8y, 37.5% male, mean LVEF 29±12%). Normalized speed at 10 QRS segments was calculated as the distance traveled by the heart vector along the QRS loop in three-dimensional space, divided by 1/10th of the QRS duration. Curvature was calculated as the magnitude of the derivative of the QRS loop tangent vector divided by speed. Planarity was calculated as the mean of the dihedral angles between 2 consecutive planes for all planes generated for the median beat. Orbital frequency (a scalar measure of rotation rate of the QRS vector) was calculated as a product of speed and curvature. RESULTS: Mixed regression analysis showed that speed was slower [6.6 (95%CI 4.4-8.9) vs. 24.6 (95%CI 11.5-37.7) microV/ms; P<0.0001]; orbital frequency was smaller [1.4 (95%CI 1.2-1.6) vs. 6.8 (95%CI 5.4-8.1) ms<sup>-1</sup>; P<0.0001], and planarity was larger by 3.6 degrees (95%CI 1.4 degrees -5.8; P=0.002) in VT cases than in healthy controls. ROC AUC for orbital frequency was 0.940 (95%CI 0.935-0.944) across all frequencies and QRS segments. ROC AUC for planarity at 70-249Hz was 0.995 (95%CI 0.985-1.00). ROC AUC for speed at 70-79Hz was 0.979 (95%CI 0.969-0.989). CONCLUSION: This novel method reveals characteristic features of an abnormal electrophysiological substrate associated with VT.

Thacker, R. W., Díaz, M. C., Kerner, A., Vignes-Lebbe, R., Segerdell, E., Haendel, M. A., et al. (2014).

The porifera ontology (PORO): Enhancing sponge systematics with an anatomy ontology. *Journal of Biomedical Semantics*, 5(1)

Background: Porifera (sponges) are ancient basal metazoans that lack organs. They provide insight into key evolutionary transitions, such as the emergence of multicellularity and the nervous system. In addition, their ability to synthesize unusual compounds offers potential biotechnical applications. However, much of the knowledge of these organisms has not previously been codified in a machine-readable way using modern web standards. Results: The Porifera Ontology is intended as a standardized coding system for sponge anatomical features currently used in systematics. The ontology is available from <http://purl.obolibrary.org/obo/poro.owl>, or from the project homepage <http://porifera-ontology.googlecode.com/>. The version referred to in this manuscript is permanently available from <http://purl.obolibrary.org/obo/poro/releases/2014-03-06/>. **Conclusions:** By standardizing character representations, we hope to facilitate more rapid description and identification of sponge taxa, to allow integration with other evolutionary database systems, and to perform character mapping across the major clades of sponges to better understand the evolution of morphological features. Future applications of the ontology will focus on creating (1) ontology-based species descriptions; (2) taxonomic keys that use the nested terms of the ontology to more quickly facilitate species identifications; and (3) methods to map anatomical characters onto molecular phylogenies of sponges. In addition to modern taxa, the ontology is being extended to include features of fossil taxa. © 2014 Thacker et al.; licensee BioMed Central Ltd.

Thornburg, K., O'Tierney, P. F., Morgan, T., & Louey, S. (2010). *The placental roots of cardiovascular disease* Cambridge University Press.

Introduction: Over the past 20 years the scientific literature has reported important relationships between placental size and augmented risk of cardiovascular disease in the offspring. The foundational paper that led to this idea was published by Barker and colleagues in 1989. They showed an inverse relationship between the mortality of men and women who lived in Hertfordshire, UK, and their weight at birth (Figure 16.1). This report was a landmark discovery; it showed clearly what many developmental biologists had previously noted – that the plastic

nature of development underlies the lifelong health of the offspring. But this finding by Barker et al. was more specific. Birth weight was discovered to be a clear, statistically reliable predictor of death from one chronic disease condition. One exciting part of the birth weight story is the detective work from which it arose. Barker's team sought the culprit responsible for high death rates from ischaemic heart disease in the north of England. For them, the geographical map was as powerful as electrophoretic gel is for the molecular biologist. The team noticed that regions in England and Wales with high mortality rates from ischaemic heart disease overlapped perfectly regions with high rates of neonatal death (reviewed by Barker). © Cambridge University Press 2011.

Thornburg, K. L. (2006). *Programming the cardiovascular system* Cambridge University Press.

Introduction David Barker and colleagues first trained the spotlight on the idea that the prenatal environment shapes the lifelong health of the heart. They reported that the standardised mortality for ischaemic heart disease within a large population of English men and women was much higher in babies born at the 5- pound (2.3 kg) end of the birthweight scale compared to babies at the 9-pound (4.0 kg) end (Barker et al., 1989). Birthweight affected the death rate in men and women similarly across the weight range, with a significant sudden upturn in the heaviest babies studied. The latter group of heavier newborn babies may have included babies that were macrosomic and born to diabetic mothers. In a separate study, Rich-Edwards and coworkers (1997) found a similar relationship among >100, 000 participants in the American Nurses study. In that study, the numbers of individuals who had symptoms for coronary disease and stroke increased with decreasing recalled birthweight. The implications of the epidemiological findings of Barker's group are enormous. Cardiovascular disease is the most devastating disease on earth and, as a category, kills more men and women than any other disease. In the USA alone, the costs to society for cardiovascular disease currently exceed \$350 billion annually. Furthermore, the rates of death due to cardiovascular events around the world are on the increase (American Heart Association 2004, World Health Organization, 2003, 2004a). Over half of all cardiovascular deaths worldwide are of women (World Health Organization 2004b, 2004c). © P. D. Gluckman and M. A. Hanson 2006 and Cambridge University Press, 2009.

Tisherman, S. A., Schmicker, R. H., Brasel, K. J., Bulger, E. M., Kerby, J. D., Minei, J. P., et al. (2015).

Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the resuscitation outcomes consortium. *Annals of Surgery*, 261(3), 586-590.

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

Togashi, K., Joffe, A. M., Sekhar, L., Kim, L., Lam, A., Yanez, D., et al. (2015). Randomized pilot trial of intensive management of blood pressure or volume expansion in subarachnoid hemorrhage (improves). *Neurosurgery*, 76(2), 125-134.

BACKGROUND: Volume expansion and hypertension are widely used for the hemodynamic management of patients with subarachnoid hemorrhage. OBJECTIVE: To investigate the feasibility, adherence, and retention in a trial of volume expansion and blood pressure manipulation to prevent delayed cerebral ischemia. METHODS: A randomized pilot trial using a 2-way factorial design allocating patients within 72 hours of subarachnoid hemorrhage to either

normovolemia (NV) or volume expansion (HV) and simultaneously to conventional (CBP) or augmented blood pressure (ABP) for 10 days. The study endpoints were protocol adherence and retention to follow-up. The quality of endpoints for a larger trial were 6-month modified Rankin Scale score, comprehensive neurobehavioral assessment, delayed cerebral ischemia, new stroke, and discharge disposition. RESULTS: Twenty patients were randomized and completed follow-up. The overall difference in daily mean intravenous fluid intake was 2099 mL (95% confidence interval [CI]: 867, 3333), HV vs NV group. The overall mean systolic blood pressure difference was 5 mm Hg (95% CI: 24.65, 14.75), ABP vs CBP group. Adverse events included death (n = 1), delayed cerebral ischemia (n = 1), and pulmonary complications (n = 3). There were no differences in modified Rankin Scale score between HV and NV (difference 0.1; 95% CI:21.26, 1.46, P = .87) or between ABP and CBP groups (20.5, 95% CI:21.78, 0.78, P = .43). Neuropsychological scores were similar between HV vs NV, but tended to be worse in ABP (576 27) vs CBP group (85 6 21, P = .04). CONCLUSION: This pilot study showed adequate feasibility and excellent retention to followup. Given the suggestion of possible worse neurobehavioral outcome with ABP, a larger trial to determine the optimal blood pressure management in this patient population is warranted. (ClinTrials.gov NCT01414894.). Copyright © 2014 by the Congress of Neurological Surgeons. Copyright © 2014 by the Congress of Neurological Surgeons.

Tommaso, C. L., Fullerton, D. A., Feldman, T., Dean, L. S., Hijazi, Z. M., Horlick, E., et al. (2014).

SCAI/AATS/ACC/STS operator and institutional requirements for transcatheter valve repair and replacement. part II. mitral valve. *Catheterization and Cardiovascular Interventions*, 84(4), 567-580.

Toupin-April, K., Barton, J., Fraenkel, L., Li, L., Grandpierre, V., Guillemin, F., et al. (2015).

Development of a draft core set of domains for measuring shared decision making in osteoarthritis: An OMERACT working group on shared decision making. *The Journal of Rheumatology*,

OBJECTIVE: Despite the importance of shared decision making for delivering patient-centered care in rheumatology, there is no consensus on how to measure its process and outcomes. The aim of this Outcome Measures in Rheumatology (OMERACT) working group is to determine the

core set of domains for measuring shared decision making in intervention studies in adults with osteoarthritis (OA), from the perspectives of patients, health professionals, and researchers.

**METHODS:** We followed the OMERACT Filter 2.0 method to develop a draft core domain set by (1) forming an OMERACT working group; (2) conducting a review of domains of shared decision making; and (3) obtaining opinions of all those involved using a modified nominal group process held at a session activity at the OMERACT 12 meeting. **RESULTS:** In all, 26 people from Europe, North America, and Australia, including 5 patient research partners, participated in the session activity. Participants identified the following domains for measuring shared decision making to be included as part of the draft core set: (1) identifying the decision, (2) exchanging information, (3) clarifying views, (4) deliberating, (5) making the decision, (6) putting the decision into practice, and (7) assessing the effect of the decision. Contextual factors were also suggested.

**CONCLUSION:** We proposed a draft core set of shared decision-making domains for OA intervention research studies. Next steps include a workshop at OMERACT 13 to reach consensus on these proposed domains in the wider OMERACT group, as well as to detail subdomains and assess instruments to develop a core outcome measurement set.

Tsuda, Y., Parkins, C. J., Caposio, P., Feldmann, F., Botto, S., Ball, S., et al. (2015). A

cytomegalovirus-based vaccine provides long-lasting protection against lethal ebola virus challenge after a single dose. *Vaccine*, 33(19), 2261-2266.

Ebola virus (Zaire ebolavirus; EBOV) is a highly lethal hemorrhagic disease virus that most recently was responsible for two independent 2014 outbreaks in multiple countries in Western Africa, and the Democratic Republic of the Congo, respectively. Herein, we show that a cytomegalovirus (CMV)-based vaccine provides durable protective immunity from Ebola virus following a single vaccine dose. This study has implications for human vaccination against ebolaviruses, as well as for development of a 'disseminating' vaccine to target these viruses in wild African great apes.

Tull, L., Crum, J., Davis, T., & Strader, C. R. (2013). *Integrating and streamlining electronic resources workflows via innovative's electronic resource management* Taylor and Francis.

Libraries have been grappling with the management of the growing number of electronic

resources, such as e-journals and electronic article indexes, for the last decade especially after the availability of many of these resources on the World Wide Web. The integrated library system wasn't originally designed to accommodate many of these functions. In 2002, Innovative Interfaces, Inc. partnered with several of their customer libraries to develop a module to manage electronic resources based on the work of the Digital Library Federation's Electronic Resources Management Initiative. The result of this partnership is a module that addresses functions such as tracking trial access, license negotiations, maintenance, troubleshooting as well as integration into the online catalog. © 2005 by The Haworth Press, Inc. All rights reserved.

Undurraga Perl, V., Diggs, B., Ham, B., & Schreiber, M. (2015). Does surgery residency prepare residents to work at critical access hospitals? *American Journal of Surgery*,  
BACKGROUND: Operations performed by surgeons working at Critical Access Hospitals (CAHs) and surgery residents have not been compared. METHODS: Procedure codes logged by general surgery residents graduating from our institution in 2013 and 2014 were obtained. Procedure codes were obtained for all CAHs in our state for 2012 to 2013. Clinically relevant categories were compared among residents and general surgeons at CAHs. RESULTS: A total of 34,246 procedures logged by general surgeons at CAHs were compared with 31,977 procedures logged by surgery residents. Endoscopy comprised 56.1% of cases done by general surgeons versus 9.1% of cases by residents ( $P < .001$ ). Excluding endoscopy, rural surgeons had higher percentages in hernia, skin/soft tissue, cholecystectomy/common bile duct, rectal/anal, and breast cases. Residents who completed a rural surgery rotation had higher numbers in small/large bowel, hernia, breast, and endoscopy. CONCLUSIONS: Surgery residency provides less exposure to endoscopy compared with a general surgery practice at CAHs. A rural rotation increases endoscopic exposure.

Urken, M. L., Milas, M., Randolph, G. W., Tufano, R., Bergman, D., Bernet, V., et al. (2015). Management of recurrent and persistent metastatic lymph nodes in well-differentiated thyroid cancer: A multifactorial decision-making guide for the thyroid cancer care collaborative. *Head and Neck*, 37(4), 605-614.  
Background Well-differentiated thyroid cancer (WDTC) recurs in up to 30% of patients.

Guidelines from the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN) provide valuable parameters for the management of recurrent disease, but fail to guide the clinician as to the multitude of factors that should be taken into account. The Thyroid Cancer Care Collaborative (TCCC) is a web-based repository of a patient's clinical information. Ten clinical decision-making modules (CDMMs) process this information and display individualized treatment recommendations. Methods We conducted a review of the literature and analysis of the management of patients with recurrent/persistent WDTC. Results Surgery remains the most common treatment in recurrent/persistent WDTC and can be performed with limited morbidity in experienced hands. However, careful observation may be the recommended course in select patients. Reoperation yields biochemical remission rates between 21% and 66%. There is a reported 1.2% incidence of permanent unexpected nerve paralysis and a 3.5% incidence of permanent hypoparathyroidism. External beam radiotherapy and percutaneous ethanol ablation have been reported as therapeutic alternatives. Radioactive iodine as a primary therapy has been reported previously for metastatic lymph nodes, but is currently advocated by the ATA as an adjuvant to surgery. Conclusion The management of recurrent lymph nodes is a multifactorial decision and is best determined by a multidisciplinary team. The CDMMs allow for easy adoption of contemporary knowledge, making this information accessible to both patient and clinician. © 2014 Wiley Periodicals, Inc. Head Neck 37: 605-614, 2015 © 2014 Wiley Periodicals, Inc.

Vacchi-Suzzi, C., Karimi, R., Kruse, D., Silbernagel, S. M., Levine, K. E., Rohlman, D. S., et al. (2015). Low-level mercury, omega-3 index and neurobehavioral outcomes in an adult US coastal population. *European Journal of Nutrition*,  
Background: Neurodevelopmental effects of omega-3 fatty acids and mercury from fish consumption have been characterized in children. In contrast, neurobehavioral outcomes associated with fish are not well studied in adults. Objective: This study of avid seafood consumers on Long Island (NY, USA) sought to define associations between mercury, seafood consumption, omega-3 fatty acids and neurobehavioral outcomes. Methods: A computer-based test system was used to assess neurobehavioral function. Blood total Hg (Hg) and omega-3 index were measured in 199 adult avid seafood eaters, who also completed the neurobehavioral assessment and an extensive food and fish frequency and demographic questionnaire. Results:

For most of the outcomes considered, neither Hg nor omega-3 index was associated with neurobehavioral outcomes after adjustment for key confounding variables. Fish consumption, however, was associated with decreased odds of both self-reported fatigue (OR 0.85; 95 % CI 0.72, 1.01) and a constellation of neurologic symptoms (OR 0.79; 95 % CI 0.66, 0.96).

Conclusions: Results from our study provide little evidence that omega-3 fatty acids or Hg is associated with cognitive function in adult avid seafood consumers. Larger studies are needed to confirm our finding of associations between fish consumption and decreased self-reported fatigue and neurologic impairment. © 2015 Springer-Verlag Berlin Heidelberg

Valerius, J., Mohan, V., Doctor, D., & Hersh, W. (2015). Collaboration leads to enhanced curriculum. *Applied Clinical Informatics*, 6(1), 200-209.

BACKGROUND: In 2007, we initiated a health information management (HIM) track of our biomedical informatics graduate program, and subsequent ongoing program assessment revealed a confluence of topics and courses within HIM and clinical informatics (CI) tracks. We completed a thorough comparative analysis of competencies derived from AMIA, AHIMA, and CAHIIM.

Coupled with the need to streamline course offerings, the process, described in this paper allowed new opportunities for faculty collaboration, resulted in the creation of a model assessment for best practice in courses, and led to new avenues of growth within the program.

OBJECTIVE: The objective of the case study is to provide others in the informatics educational community with a model for analysis of curriculum in order to improve quality of student learning.

METHODS: We describe a case study where an academic informatics program realigned its course offerings to better reflect the HIM of today, and prepare for challenges of the future.

Visionary leadership, intra-departmental self-analysis and alignment of the curriculum through defined mapping process reduced overlap within the CI and HIM tracks. Teaching within courses was optimized through the work of core faculty collaboration.

RESULTS: The analysis of curriculum resulted in reduction of overlap within course curriculum. This allowed for additional and new course content to be added to existing courses.

CONCLUSIONS: Leadership fostered an environment where top-down as well as bottom-up collaborative assessment activities resulted in a model to consolidate learning and reduce unnecessary duplication within courses. A focus on curriculum integration, emphasis on course alignment and strategic consolidation of course

content raised the quality of informatics education provided to students. Faculty synergy was an essential component of this redesign process. Continuous quality improvement strategy included an ongoing alignment of curriculum and competencies through a comparative analysis approach. Through these efforts, new innovation was possible.

Van, P. Y., Sambasivan, C. N., Wade, C. E., Jones, J. A., Holcomb, J. B., Schreiber, M. A., et al.

(2010). High transfusion ratios are not associated with increased complication rates in patients with severe extremity injuries. *The Journal of Trauma*, 69, S64-S68.

BACKGROUND: High transfusion ratios of plasma to packed red blood cells (>1:2) have been associated with increased survival and increased complications in patients receiving massive transfusion (MT). We hypothesized that high ratio transfusion would be associated with no survival benefit and increased complications in combat victims with compressible hemorrhage.

METHODS: A retrospective analysis of soldiers injured in the current conflict during 5 years (n = 2,105) who received blood was performed on those with isolated extremity (abbreviated injury scale extremity score > or = 3 and abbreviated injury scale score 0-2 in all other regions) injury comparing those who received a MT with those who did not. Transfusion ratios in the first 24 hours were correlated with outcomes. RESULTS: Injury severity score (14.6 vs. 12.1; p 0.05). In those receiving a non-MT, high ratios were associated with similar mortality (4.8% vs. 3.9%; p > 0.05) and complications (12.4% vs. 9.2%; p > 0.05). CONCLUSIONS: Extremity injured patients receiving MT may benefit from high transfusion ratios and do not experience increased complications. No change in mortality or complications was observed in non-MT patients across transfusions ratios. High transfusion ratios are not associated with increased complications in patients with isolated extremity injury regardless of whether a MT is required.

Ventres, W. B. (2015). The Q-list manifesto: How to get things right in generalist medical practice.

*Families, Systems and Health*, 33(1), 5-13.

Checklists have become popular in medical practice since the publication of surgeon Atul Gawande's book, *The Checklist Manifesto: How to Get Things Right*. Based on his 26 years of practice as a family physician and informed by scholarly works from other professional disciplines, the author suggests that although checklists are helpful for promoting habitual

reflection, they are limited in scope and meaning, and more suited for procedural undertakings than the bio-psycho-social-existential orientation of generalist practice. The author reviews the characteristics of generalist practice and suggests that clinicians develop a list of questions to help them recall and examine concepts key to the exploration and management of routine and challenging situations with patients. He proposes his own Question-List, or Q-List, and recommends its adaptation for use as a manifesto to the rich and engaging work of generalist medicine. © 2015 American Psychological Association.

Ventres, W. B., & Wilson, C. L. (2015). Beyond ethical and curricular guidelines in global health: Attitudinal development on international service-learning trips. *BMC Medical Education, 15*, 68-015-0357-7.

**BACKGROUND:** Health professionals from high-income countries are increasingly becoming involved in international service-learning trips in low and low/middle-income countries. While much has been written about the ethics and curricular guidelines related to such endeavors, scant attention has been paid to the attitudes with which trainees and clinicians enter into or return from them. In this essay the authors explore how attitudes contribute to the success or failure of international service-learning trips. **DISCUSSION:** The authors submit that the attitudes with which visiting health professionals approach international service-learning trips are much more critical to the success of these experiences than their demonstrated knowledge base or specialized skill sets. They list five attitudes that can aid those participating in international service-learning trips. They list five troubling attitudes that, while common, those participating in international service-learning trips can learn to recognize and avoid. They suggest five strategies key to learning respectful attitudes that can foster success in such cross-cultural activities. Lastly, the authors review several concepts related to attitude development in short or long-term global health work. The attitudes with which visiting health professionals approach international service-learning activities can be important components of the success or failure of the experiences. Through thoughtful consideration of attitudes and approaches, participants on such trips can build a framework for rich and rewarding experiences in global medicine and global health.

Verro, P., & Wong, V. S. (2015). Phentermine association with a case of hemorrhagic posterior reversible encephalopathy syndrome. *The Neurologist*, *19*(4), 119-120.

Verstovsek, S., Mesa, R. A., Gotlib, J., Levy, R. S., Gupta, V., Dipersio, J. F., et al. (2015). Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: Results of a median 3-year follow-up of COMFORT-I. *Haematologica*, *100*(4), 479-488.

In the phase III COMFORT-I study, the Janus kinase 1 (JAK1)/JAK2 inhibitor ruxolitinib provided significant improvements in splenomegaly, key symptoms, and quality-of-life measures and was associated with an overall survival benefit relative to placebo in patients with intermediate-2 or high-risk myelofibrosis. This planned analysis assessed the long-term efficacy and safety of ruxolitinib at a median follow-up of 149 weeks. At data cutoff, approximately 50% of patients originally randomized to ruxolitinib remained on treatment whereas all patients originally assigned to placebo had discontinued or crossed over to ruxolitinib. At week 144, mean spleen volume reduction was 34% with ruxolitinib. Previously observed improvements in quality-of-life measures were sustained with longer-term ruxolitinib therapy. Overall survival continued to favor ruxolitinib despite the majority of placebo patients crossing over to ruxolitinib [hazard ratio 0.69 (95% confidence interval: 0.46-1.03); P=0.067]. Exploratory analyses suggest that crossover may have contributed to an underestimation of the true survival difference between the treatment groups. Ruxolitinib continued to be generally well tolerated; there was no pattern of worsening grade  $\geq 3$  anemia or thrombocytopenia with longer-term ruxolitinib exposure. These longer-term data continue to support the efficacy and safety of ruxolitinib in patients with myelofibrosis. © 2015 Ferrata Storti Foundation.

Vogt, S., Gleber, S. -, Jin, Q., Chen, S., Finney, L., Jacobsen, C., et al. (2014). Biological X-ray fluorescence microscopy: Advances and unique opportunities. *Microscopy and Microanalysis*, *20*(3), 1306-1307.

Voss, H. C., Mathews, L. R., Fossen, T., Scott, G., & Schaefer, M. (2015). Community-academic partnerships: Developing a service-learning framework. *Journal of Professional Nursing*, Academic partnerships with hospitals and health care agencies for authentic clinical learning have become a major focus of schools of nursing and professional nursing organizations. Formal

academic partnerships in community settings are less common despite evolving models of care delivery outside of inpatient settings. Community-Academic partnerships are commonly developed as a means to engage nursing students in service-learning experiences with an emphasis on student outcomes. The benefit of service-learning projects on community partners and populations receiving the service is largely unknown primarily due to the lack of structure for identifying and measuring outcomes specific to service-learning. Nursing students and their faculty engaged in service-learning have a unique opportunity to collaborate with community partners to evaluate benefits of service-learning projects on those receiving the service. This article describes the development of a service-learning framework as a first step toward successful measurement of the benefits of undergraduate nursing students' service-learning projects on community agencies and the people they serve through a collaborative community-academic partnership. © 2015.

Vranka, J. A., Bradley, J. M., Yang, Y. F., Keller, K. E., & Acott, T. S. (2015). Mapping molecular differences and extracellular matrix gene expression in segmental outflow pathways of the human ocular trabecular meshwork. *PloS One*, *10*(3), e0122483.

Elevated intraocular pressure (IOP) is the primary risk factor for glaucoma, and lowering IOP remains the only effective treatment for glaucoma. The trabecular meshwork (TM) in the anterior chamber of the eye regulates IOP by generating resistance to aqueous humor outflow. Aqueous humor outflow is segmental, but molecular differences between high and low outflow regions of the TM are poorly understood. In this study, flow regions of the TM were characterized using fluorescent tracers and PCR arrays. Anterior segments from human donor eyes were perfused at physiological pressure in an ex vivo organ culture system. Fluorescently-labeled microspheres of various sizes were perfused into anterior segments to label flow regions. Actively perfused microspheres were segmentally distributed, whereas microspheres soaked passively into anterior segments uniformly labeled the TM and surrounding tissues with no apparent segmentation. Cell-tracker quantum dots (20 nm) were localized to the outer uveal and corneoscleral TM, whereas larger, modified microspheres (200 nm) localized throughout the TM layers and Schlemm's canal. Distribution of fluorescent tracers demonstrated a variable labeling pattern on both a macro- and micro-scale. Quantitative PCR arrays allowed identification of a variety of extracellular matrix

genes differentially expressed in high and low flow regions of the TM. Several collagen genes (COL16A1, COL4A2, COL6A1 and 2) and MMPs (1, 2, 3) were enriched in high, whereas COL15A1, and MMP16 were enriched in low flow regions. Matrix metalloproteinase activity was similar in high and low regions using a quantitative FRET peptide assay, whereas protein levels in tissues showed modest regional differences. These gene and protein differences across regions of the TM provide further evidence for a molecular basis of segmental flow routes within the aqueous outflow pathway. New insight into the molecular mechanisms of segmental aqueous outflow may aid in the design and delivery of improved treatments for glaucoma patients.

Vranka, J. A., Kelley, M. J., Acott, T. S., & Keller, K. E. (2015). Extracellular matrix in the trabecular meshwork: Intraocular pressure regulation and dysregulation in glaucoma. *Experimental Eye Research*, 133, 112-125.

The trabecular meshwork (TM) is located in the anterior segment of the eye and is responsible for regulating the outflow of aqueous humor. Increased resistance to aqueous outflow causes intraocular pressure to increase, which is the primary risk factor for glaucoma. TM cells reside on a series of fenestrated beams and sheets through which the aqueous humor flows to exit the anterior chamber via Schlemm's canal. The outer trabecular cells are phagocytic and are thought to function as a pre-filter. However, most of the outflow resistance is thought to be from the extracellular matrix (ECM) of the juxtacanalicular region, the deepest portion of the TM, and from the inner wall basement membrane of Schlemm's canal. It is becoming increasingly evident that the extracellular milieu is important in maintaining the integrity of the TM. In glaucoma, not only have ultrastructural changes been observed in the ECM of the TM, and a significant number of mutations in ECM genes been noted, but the stiffness of glaucomatous TM appears to be greater than that of normal tissue. Additionally, TGFbeta2 has been found to be elevated in the aqueous humor of glaucoma patients and is assumed to be involved in ECM changes deep with the juxtacanalicular region of the TM. This review summarizes the current literature on trabecular ECM as well as the development and function of the TM. Animal models and organ culture models targeting specific ECM molecules to investigate the mechanisms of glaucoma are described. Finally, the growing number of mutations that have been identified in ECM genes and genes that modulate ECM in humans with glaucoma are documented.

Wagner, D. V., Stoeckel, M., E Tudor, M., & Harris, M. A. (2015). Treating the most vulnerable and costly in diabetes. *Current Diabetes Reports*, 15(6), 606-015-0606-5.

Diabetic ketoacidosis (DKA) is associated with negative health outcomes and high costs for patients, families, and communities. Interventions developed to effectively reduce DKA and related costs should target the multiple risk factors associated with DKA and adherence difficulties. Certain demographic, psychological, and family factors are associated with increased risk for adherence problems and DKA. Individuals with a combination of risk factors (e.g., mental health problems, low socioeconomic status, high family conflict) may be particularly vulnerable to DKA. Although several different interventions have demonstrated promise in improving adherence and/or decreasing the risk of DKA, the generalizability of treatment results to those individuals most vulnerable to DKA is limited. Approaches which include multiple evidence-based components of care, are flexible in treatment delivery (e.g., home- and community-based, utilize technology), and target the multiple risk factors across relevant systems (e.g., individual, family, school, medical) are warranted to effectively reduce DKA in vulnerable populations.

Walter, N. A., McWeeney, S. K., Peters, S. T., Belknap, J. K., Hitzemann, R., & Buck, K. J. (2008).

Single-nucleotide polymorphism masking. *Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism*, 31(3), 270-271.

Microarrays are widely used to evaluate gene expression at the genome scale. However, all too often the importance of data analysis at the level of the individual probe is overlooked. This is a particular problem when trying to detect differences in gene expression levels among genetically unique animals, across inbred animal strains, or among genetically modified animals. Of particular concern is the presence of small modifications in the DNA (i.e., single nucleotide polymorphisms [SNPs]) that occur naturally and differentiate one individual from the next. This article describes the potential impact of SNPs on analyses of gene expression differences and introduces an approach called SNP masking, which implements removal of SNP-affected probes. SNP masking is a valuable and feasible approach that can ameliorate these hybridization problems.

Warrick, J. I., Hovelson, D. H., Amin, A., Liu, C. -, Cani, A. K., McDaniel, A. S., et al. (2015). Tumor evolution and progression in multifocal and paired non-invasive/invasive urothelial carcinoma. *Virchows Archiv*, 466(3), 297-311.

Although multifocal tumors and non-invasive/invasive components are commonly encountered in surgical pathology, their genetic relationship is often poorly characterized. We used next-generation sequencing (NGS) to characterize somatic alterations in a patient with five spatially distinct, high-grade papillary urothelial carcinomas (UCs), with one tumor harboring an underlying invasive component. NGS of 409 cancer-related genes was performed on DNA isolated from formalin-fixed paraffin-embedded (FFPE) blocks representing each papillary tumor (n = 5), the invasive component of one tumor, and matched normal tissue. We identified nine unique non-synonymous somatic mutations across the six UC samples, including five present in each carcinoma sample, consistent with clonal origin and limited intertumoral heterogeneity. Copy number and loss of heterogeneity (LOH) profiles were similar in all six carcinomas; however, the invasive carcinoma component uniquely showed focal CDKN2A loss and chromosome 9 LOH and did not harbor gains of chromosomes 5p or X that were present in the other tumor samples. Phylogenetic analysis supported the invasive component arising from a shared progenitor prior to the outgrowth of cells in the non-invasive tumors. Results were extended to three additional cases of upper tract UC with paired non-invasive/invasive components, which identified driving alterations exclusive to both non-invasive and invasive components. Lastly, we performed targeted RNA sequencing (RNAseq) using a custom bladder cancer panel, which confirmed gene expression signature differences between paired non-invasive/invasive components. The results and approaches presented here may be useful in understanding the clonal relationships in multifocal cancers or paired non-invasive/invasive components from routine FFPE specimens. © 2014, Springer-Verlag Berlin Heidelberg.

Watabe, M., Kato, T. A., Teo, A. R., Horikawa, H., Tateno, M., Hayakawa, K., et al. (2015).

Relationship between trusting behaviors and psychometrics associated with social network and depression among young generation: A pilot study. *PLoS One*, 10(3), e0120183.

Maladaptive social interaction and its related psychopathology have been highlighted in psychiatry especially among younger generations. In Japan, novel expressive forms of psychiatric

phenomena such as "modern-type depression" and "hikikomori" (a syndrome of severe social withdrawal lasting for at least six months) have been reported especially among young people. Economic games such as the trust game have been utilized to evaluate real-world interpersonal relationships as a novel candidate for psychiatric evaluations. To investigate the relationship between trusting behaviors and various psychometric scales, we conducted a trust game experiment with eighty-one Japanese university students as a pilot study. Participants made a risky financial decision about whether to trust each of 40 photographed partners. Participants then answered a set of questionnaires with seven scales including the Lubben Social Network Scale (LSNS)-6 and the Patient Health Questionnaire (PHQ)-9. Consistent with previous research, male participants trusted partners more than female participants. Regression analysis revealed that LSNS-family (perceived support from family) for male participants, and item 8 of PHQ-9 (subjective agitation and/or retardation) for female participants were associated with participants' trusting behaviors. Consistent with claims by social scientists, our data suggest that, for males, support from family was negatively associated with cooperative behavior toward non-family members. Females with higher subjective agitation (and/or retardation) gave less money toward males and high attractive females, but not toward low attractive females in interpersonal relationships. We believe that our data indicate the possible impact of economic games in psychiatric research and clinical practice, and validation in clinical samples including modern-type depression and hikikomori should be investigated.

Wax, M. K., Futran, N. D., Rosenthal, E. L., Blackwell, K. E., & Cannady, S. (2015). Accidental dropping or misplacement of free flaps. *The Laryngoscope*,  
OBJECTIVES/HYPOTHESIS: Standard operating procedures have been developed in many surgical practices to ensure quality of care as it relates to specimens removed from the body. Most of these specimens are sent to pathology. Some, such as calvarial bone harvested during craniotomy are replaced in the body. Free tissue transfer involves harvesting tissue from one body site, storage for a variable period of time outside of the body, and then insertion in another location. As with any system there is ample opportunity for accidental "misplacement." We undertook a multi-institutional study to examine the incidence, etiology, and opportunity for process improvement. STUDY DESIGN: Retrospective review. METHODS: A retrospective review

was performed at five institutions (8,382 free flaps). RESULTS: Thirteen (0.15%) flaps were dropped or wrapped in a towel/sponge and placed in a waste bucket. Eight radial forearm, three fibula, one latissimus dorsi, and one anterolateral thigh flap were misplaced. All flaps were retrieved, washed in saline/betadine, and implanted into the patient. All flaps survived; no altered outcomes were encountered. The etiology of the misplacement of the free tissue from the sterile field included miscommunication among nursing staff (seven), miscommunication among medical staff (two), and dropping the flap (four). As a result of these events, changes in the handling procedures were instituted including standard labeling methodologies and communication strategies. CONCLUSIONS: Inadvertent misplacement of free tissue from the sterile field does occur in a sporadic fashion. Process improvement evaluation at all institutions led to improved strategies for prevention. No long-lasting altered outcomes were encountered. LEVEL OF EVIDENCE: 4 Laryngoscope, 2015.

Webb, B. C., Whittle, T., & Schwarz, E. (2015). Oral health and dental care in aged care facilities in new south wales, australia. part 3 concordance between residents' perceptions and a professional dental examination. *Gerodontology*,

Objectives: To determine the perceptions of dental care held by the residents in aged care facilities (ACFs) in New South Wales (NSW) and to compare these perceptions with clinical observations. Background: No specific data exist relating to NSW residents' perceptions of dental care compared with a clinical examination. Planning for appropriate oral health programs in ACFs necessitate such data. Materials and methods: Four Area Health Services of Sydney and 25 low care ACFs were selected from which representative residents were sampled who completed a survey and underwent a basic dental examination. Results: Of the subjects (25 males, 96 females), 76.9% had never received a dental visit as entering the ACF; 14.1% suffered from dental pain; 69.4% wore dentures and of these 18.3% required assistance in cleaning. Dentures were cleaned twice/day in 54.9% of cases. Natural teeth were reported present in 71.9% of residents, and 85.1% did not require assistance in cleaning. Appropriate dental care facilities and dry mouth were most frequent problems highlighted. Clinical examinations showed that 69% were denture wearers; oral hygiene and denture hygiene were considered good in 15.7% of cases. A high level of concordance existed between self-reports and examination. Conclusions:

Increased awareness about oral health across leadership, caregivers and residents with appropriate dental health education and dedicated space within facilities would provide a much needed improvement for addressing oral health issues of the ACF residents. This might be the right time to plan for the future challenges that will need to be met by the NSW care system. © 2015 John Wiley & Sons A/S and The Gerodontology Association.

Williams, C. D., Chan, A. T., Elman, M. R., Kristensen, A. H., Miser, W. F., Pignone, M. P., et al.

(2015). Aspirin use among adults in the u.s.: Results of a national survey. *American Journal of Preventive Medicine*, 48(5), 501-508.

INTRODUCTION: The use of aspirin in patients without cardiovascular disease remains controversial. Patients' understanding of the risks and benefits of aspirin likely contribute to the decision of whether or not to use aspirin regularly. The purpose of this study is to assess patients' knowledge of aspirin and identify factors contributing to regular use. METHODS: A survey of U.S. adults aged 45-75 years was performed to ascertain aspirin use and factors that may be associated with use. Multivariate logistic regression was used to identify predictors of current use of aspirin among those with a primary prevention indication. The survey was completed in 2012 with data analysis performed in 2013. RESULTS: Among 2,509 respondents, 52% reported current aspirin use. Among 2,039 respondents without a history of cardiovascular disease, current use of aspirin was 47%. Regular use of aspirin for primary prevention was associated with the presence of major cardiovascular disease risk factors (OR=3.0, 95% CI=2.4, 3.7), high self-assessed knowledge of aspirin (OR=9.1, 95% CI=5.2, 15.7), and having discussed aspirin therapy with a provider (OR=25.9, 95% CI=19.7, 34.1). Several markers of healthy lifestyle choices were also associated with regular use. After multivariate analysis, the strongest independent predictor of regular aspirin use was having discussed aspirin therapy with a provider (OR=23.79, 95% CI=17.8, 31.5). CONCLUSIONS: Approximately half of the nationwide survey of U.S. adults reported regular aspirin use. Among those with a primary prevention indication, having discussed aspirin with a provider was the strongest predictor of regular use.

Williams, E. M., Higgins, J. P., Sangoi, A. R., McKenney, J. K., & Troxell, M. L. (2015). Androgen receptor immunohistochemistry in genitourinary neoplasms. *International Urology and*

*Nephrology*, 47(1), 81-85.

Results: Androgen receptor was positive in 95 % of prostate carcinomas (n = 230), but 19 % of invasive urothelial carcinomas of the bladder (n = 190) and 33 % of non-invasive bladder urothelial carcinomas were also AR positive (N = 107). Furthermore, 16 % of renal pelvis urothelial carcinomas (n = 43) were positive. Of primary renal cell carcinomas, 19 % were AR positive (n = 307). From a metastatic renal cell carcinoma cohort, 28 % of metastases were AR positive (N = 126). Six percent of non-teratomatous testicular germ cell tumors stained for AR (n = 103). Purpose: Androgen receptor (AR) is a recognized immunohistochemical marker of prostate cancer. However, the sensitivity and specificity of AR for prostate cancer in the setting of other genitourinary neoplasms has not been rigorously studied. Methods: We employed tissue microarrays containing prostate carcinomas, urothelial carcinomas, renal cell carcinomas, and testicular neoplasms. Slides were stained immunohistochemically for AR. Conclusions: Our data show that the sensitivity of AR immunohistochemistry for prostate cancer is 94.8 %. However, the specificity of AR is only 81.4 %, among our cohort of invasive genitourinary tumors. Thus, we find the specificity of AR suboptimal, yet AR may remain useful as a component of an immunostain panel. © 2014, Springer Science+Business Media Dordrecht.

Wood, P. L., Barnette, B. L., Kaye, J. A., Quinn, J. F., & Woltjer, R. L. (2015). Non-targeted lipidomics of CSF and frontal cortex grey and white matter in control, mild cognitive impairment, and alzheimer's disease subjects. *Acta Neuropsychiatrica*, , 1-9.

OBJECTIVE: We undertook a non-targeted lipidomics analysis of post-mortem cerebrospinal fluid (CSF), frontal cortex grey matter, and subjacent white matter to define potential biomarkers that distinguish cognitively intact subjects from those with incipient or established dementia. Our objective was to increase our understanding of the role of brain lipids in pathophysiology of aging and age-related cognitive impairment. METHODS: Levels of 650 individual lipids, across 26 lipid subclasses, were measured utilising a high-resolution mass spectrometric analysis platform.

RESULTS: Monoacylglycerols (MAG), diacylglycerols (DAG), and the very-long-chain fatty acid 26:0 were elevated in the grey matter of the mild cognitive impairment (MCI) and old dementia (OD) cohorts. Ethanolamine plasmalogens (PlsEtn) were decreased in the grey matter of the young dementia (YD) and OD cohorts while and phosphatidylethanolamines (PtdEth) were lower

in the MCI, YD and OD cohorts. In the white matter, decrements in sulphatide levels were detected in the YD group, DAG levels were elevated in the MCI group, and MAG levels were increased in the YD and OD groups. CONCLUSION: The parallel changes in grey matter MAGs and DAGs in the MCI and OD groups suggest that these two cohorts may have a similar underlying pathophysiology; consistent with this, MCI subjects were more similar in age to OD than to YD subjects. While PlsEtn and phosphatidylethanolamine were decreased in the YD and OD groups they were unaltered in the MCI group indicating that alterations in plasmalogen synthesis are unlikely to represent an initiating event in the transition from MCI to dementia.

Woody, G., Bruce, D., Korthuis, P. T., Chhatre, S., Hillhouse, M., Jacobs, P., et al. (2014). Authors' reply: "risk reduction with buprenorphine-naloxone and methadone: Patient's choice". *Journal of Acquired Immune Deficiency Syndromes*, 67(5), e142-e143.

Wray, L., Vujkovic, M., McWilliams, T., Cannon, S., Devidas, M., Stork, L., et al. (2014). TPMT and MTHFR genotype is not associated with altered risk of thioguanine-related sinusoidal obstruction syndrome in pediatric acute lymphoblastic leukemia: A report from the children's oncology group. *Pediatric Blood and Cancer*, 61(11), 2086-2088.

Sinusoidal obstruction syndrome is a complication of therapy for pediatric ALL and may be modified by thiopurine methyltransferase activity as well as by MTHFR genotype. We assessed TPMT \*3A, \*3B, \*3C, and MTHFR C677T and A1298C germline genetic polymorphisms among 351 patients enrolled in the thioguanine treatment arm of CCG-1952 clinical trial. TPMT and MTHFR C677T genotypes were not associated with SOS risk. The combination of MTHFR and TPMT variant genotypes was not associated with SOS risk. These suggest that germline genetic variation in TPMT and MTHFR do not significantly alter SOS risk in patients exposed to thioguanine. © 2014 Wiley Periodicals, Inc.

Yadav, V., Shinto, L., & Bourdette, D. N. (2011). *Complementary and alternative treatments in multiple sclerosis* Cambridge University Press.

Introduction Despite recent therapeutic advances, multiple sclerosis (MS) remains a chronic disabling disease with no cure. National surveys have demonstrated the widespread use of complementary and alternative medicine (CAM) among the general population in the United

States, and that individuals with a variety of chronic illnesses are more likely to use CAM than the general population., Several surveys have demonstrated that individuals with MS often explore CAM treatment options.– Neurologists have long recognized that many individuals with MS use alternative therapies but generally have taken little interest in these therapies. Individuals with MS and neurologists frequently adopt a “don't ask, don't tell” policy regarding alternative therapies. Neurologists are sometimes very negative about patient use of alternative therapies primarily for two reasons: first, they cite the lack of scientific evidence establishing efficacy for various CAM therapies; second, they focus on highly publicized therapies that are expensive, seemingly bizarre or even dangerous, such as replacement of amalgam dental fillings, magnet therapy, and bees stings, as being representative of CAM therapies and want to protect their patients from pointless expenses and risks. However, these negative attitudes are not well founded. First, despite individuals with MS reporting benefit from some alternative therapies, there has been a paucity of scientifically valid research on CAM therapies for MS. The lack of scientific evidence on efficacy does not mean that there is no benefit; we simply do not have the data to allow us to determine what works and what does not. Second, most individuals with MS who use CAM therapies tend to use affordable and low-risk treatments, such as diet therapies, nutritional supplements, herbal therapies, and mind–body therapies, such as yoga and prayer.– While there certainly are individuals with MS who make poor decisions regarding CAM use, in general, individuals with MS who use CAM seem to be sensible in their approach. Rather than ignoring the issue or adopting a universally negative attitude about CAM, neurologists should be better informed about CAM use so that they can serve as a resource for these individuals. © Cambridge University Press 2011.

Zapata, D. F., Howard, L. E., Aronson, W. J., Kane, C. J., Terris, M. K., Amling, C. L., et al. (2015).

Smoking is a predictor of adverse pathological features at radical prostatectomy: Results from the shared equal access regional cancer hospital database. *International Journal of Urology*, Objective: To test the relationship of smoking and aggressive prostate cancer in men undergoing radical prostatectomy. Methods: A retrospective analysis of 2290 men who underwent radical prostatectomy from the Shared Equal Access Regional Cancer Hospital database from 2000 to 2013 was carried out. There were 1592 (70%) non-smokers and 698 (30%) smokers at radical

prostatectomy. Logistic regression was used to examine whether smoking predicted Gleason score ( $\geq 4+3$ ), margin status, extracapsular extension or seminal vesicle invasion. Linear regression was used to test the relationship between smoking and tumor volume. Results: Smokers were younger, more likely to be black, had lower body mass index, higher pathological Gleason score, more positive margins and extracapsular extension (all  $P < 0.05$ ) versus non-smokers. On crude analysis, smoking was associated with positive margins (odds ratio 1.32;  $P = 0.003$ ) and extracapsular extension (odds ratio 1.26;  $P = 0.036$ ). After adjusting for multiple clinical factors, smoking remained associated with a 19-35% increased risk of every adverse feature studied, though only the association with extracapsular extension reached significance. On multivariable analysis, a trend for smokers to have larger tumor volumes (geometric mean 5.8 vs 5.3g;  $P = 0.062$ ) was found. Conclusions: In patients undergoing radical prostatectomy, there seems to be a trend for smokers to have worse pathological features compared with non-/former smokers. If confirmed in future studies, smoking should be considered a modifiable risk factor for aggressive prostate cancer. © 2015 The Japanese Urological Association.

Zhang, C., Bosch, M. A., Qiu, J., Rønnekleiv, O. K., & Kelly, M. J. (2015). Rapid communication: 17 $\beta$ -estradiol increases persistent  $Na^+$  current and excitability of AVPV/PeN kiss1 neurons in female mice. *Molecular Endocrinology*, 29(4), 518-527.

In vitro slice studies have revealed that there are significant differences in the spontaneous firing activity between anteroventral periventricular/periventricular preoptic nucleus (AVPV/PeN) and arcuate nucleus (ARC) kisspeptin (Kiss1) neurons in females. Although both populations express similar endogenous conductances, we have discovered that AVPV/PeN Kiss1 neurons express a subthreshold, persistent sodium current (INaP) that dramatically alters their firing activity. Based on whole-cell recording of Kiss1-Cre-green fluorescent protein (GFP) neurons, INaP was 4-fold greater in AVPV/PeN vs ARC Kiss1 neurons. An LH surge-producing dose of 17 $\beta$ -estradiol (E2) that increased Kiss1 mRNA expression in the AVPV/PeN, also augmented INaP in AVPV/PeN neurons by 2-fold. Because the activation threshold for INaP was close to the resting membrane potential (RMP) of AVPV/PeN Kiss1 neurons (-54 mV), it rendered them much more excitable and spontaneously active vs ARC Kiss1 neurons (RMP -66 mV). Single-cell RT-PCR revealed that AVPV/PeN Kiss1 neurons expressed the requisite sodium channel  $\alpha$ -subunit transcripts, NaV1.1,

NaV1.2, and NaV1.6 and  $\beta$  subunits,  $\beta 2$  and  $\beta 4$ . Importantly, NaV1.1a and  $\beta 2$  transcripts in AVPV/PeN, but not ARC, were up-regulated 2- to 3-fold by a surge-producing dose of E2, similar to the transient calcium current channel subunit Cav 3.1. The transient calcium current collaborates with INaP to generate burst firing, and selective blockade of INaP by riluzole significantly attenuated rebound burst firing and spontaneous activity. Therefore, INaP appears to play a prominent role in AVPV/ PeN Kiss1 neurons to generate spontaneous, repetitive burst firing, which is required for the high-frequency-stimulated release of kisspeptin for exciting GnRH neurons and potentially generating the GnRH surge. © 2015 by the Endocrine Society.

Zhang, J., Chen, S., Hou, Z., Cai, J., Dong, M., & Shi, X. (2015). Lipopolysaccharide-induced middle ear inflammation disrupts the cochlear intra-strial fluid-blood barrier through down-regulation of tight junction proteins. *PLoS One*, 10(3), e0122572.

Middle ear infection (or inflammation) is the most common pathological condition that causes fluid to accumulate in the middle ear, disrupting cochlear homeostasis. Lipopolysaccharide, a product of bacteriolysis, activates macrophages and causes release of inflammatory cytokines. Many studies have shown that lipopolysaccharides cause functional and structural changes in the inner ear similar to that of inflammation. However, it is specifically not known how lipopolysaccharides affect the blood-labyrinth barrier in the stria vascularis (intra-strial fluid-blood barrier), nor what the underlying mechanisms are. In this study, we used a cell culture-based in vitro model and animal-based in vivo model, combined with immunohistochemistry and a vascular leakage assay, to investigate lipopolysaccharide effects on the integrity of the mouse intra-strial fluid-blood barrier. Our results show lipopolysaccharide-induced local infection significantly affects intra-strial fluid-blood barrier component cells. Pericytes and perivascular-resident macrophage-like melanocytes are particularly affected, and the morphological and functional changes in these cells are accompanied by substantial changes in barrier integrity. Significant vascular leakage is found in the lipopolysaccharide treated-animals. Consistent with the findings from the in vivo animal model, the permeability of the endothelial cell monolayer to FITC-albumin was significantly higher in the lipopolysaccharide-treated monolayer than in an untreated endothelial cell monolayer. Further study has shown the lipopolysaccharide-induced inflammation to have a major effect on the expression of tight junctions in the blood barrier.

Lipopolysaccharide was also shown to cause high frequency hearing loss, corroborated by previous reports from other laboratories. Our findings show lipopolysaccharide-evoked middle ear infection disrupts inner ear fluid balance, and its particular effects on the intra-strial fluid-blood barrier, essential for cochlear homeostasis. The barrier is degraded as the expression of tight junction-associated proteins such as zona occludens 1, occludin, and vascular endothelial cadherin are down-regulated.

Zhang, R. R., Zheng, Y. W., Li, B., Tsuchida, T., Ueno, Y., Nie, Y. Z., et al. (2015). Human hepatic stem cells transplanted into a fulminant hepatic failure alb-TRECK/SCID mouse model exhibit liver reconstitution and drug metabolism capabilities. *Stem Cell Research & Therapy*, 6(1), 49-015-0038-9.

INTRODUCTION: Chimeric mice with humanized livers were recently established by transplanting human hepatocytes. This mouse model that is repopulated with functional human hepatocytes could be a useful tool for investigating human hepatic cell biology and drug metabolism and for other preclinical applications. Successfully transplanting human hepatocytes into mice requires that recipient mice with liver failure do not reject these human cells and provide a suitable microenvironment (supportive niche) to promote human donor cell expansion and differentiation. To overcome the limitations of current mouse models, we used Alb-TRECK/SCID mice for in vivo human immature hepatocyte differentiation and humanized liver generation. METHODS: 1.5 mug/kg diphtheria toxin was administrated into 8-week-old Alb-TRECK/SCID mice, and the degree of liver damage was assessed by serum aspartate aminotransferase activity levels. Forty-eight hours later, mice livers were sampled for histological analyses, and the human donor cells were then transplanted into mice livers on the same day. Chimeric rate and survival rate after cell transplantation was evaluated. Expressions of human hepatic-related genes were detected. A human albumin enzyme-linked immunosorbent assay was performed after 50 days of transplantation. On day 60 after transplantation, drug metabolism was examined in mice. RESULTS: Both human primary fetal liver cells and hepatic stem cells were successfully repopulated in the livers of Alb-TRECK/SCID mice that developed lethal fulminant hepatic failure after administering diphtheria toxin; the repopulation rate in some mice was nearly 100%. Compared with human primary fetal liver cells, human hepatic stem cell transplantation rescued

Alb-TRECK/SCID mice with lethal fulminant hepatic failure, and human hepatic stem cell-derived humanized livers secreted more human albumin into mouse sera and also functioned as a "human liver" that could metabolize the drugs ketoprofen and debrisoquine. CONCLUSION: Our model of a humanized liver in Alb-TRECK/SCID mice may provide for functional applications such as drug metabolism, drug to drug interactions, and promote other in vivo and in vitro studies.

Zhu, M., Ashraf, M., Zhang, Z., Streiff, C., Shimada, E., Kimura, S., et al. (2015). Real time three-dimensional echocardiographic evaluations of fetal left ventricular stroke volume, mass, and myocardial strain: In vitro and in vivo experimental study. *Echocardiography (Mount Kisco, N.Y.)*, BACKGROUND: Left ventricular stroke volume, mass, and myocardial strain are valuable indicators of fetal heart function. This study investigated the feasibility of nongated real time three-dimensional echocardiography (RT3DE) to determine fetal stroke volume (SV), left ventricular mass (LVM), and myocardial strain under different conditions. METHODS: To evaluate fetal hearts, fetal-sized rabbit hearts were used in this study. The in vitro portion of this study was carried out using a balloon inserted into the LV of eight fresh rabbit hearts and driven by a calibrated pulsatile pump. RT3DE volumes were obtained at various pump-set SVs. The in vivo experiments in this study were performed on open-chest rabbits. RT3DE volumes were acquired at the following conditions: baseline, simulated hypervolemia, inferior vena cava (IVC) ligation, and ascending aorta (AAO) ligation. Displacement values and sonomicrometry data were used as references for RT3DE-derived SV, LVM, longitudinal strain (LS), and circumferential strain (CS). RESULTS: Excellent correlations between RT3DE-derived values and reference values were demonstrated and accompanied by high coefficients of determination ( $R^2$ ) for both in vitro and in vivo studies for SV, LVM, LS, and CS (in vitro: SV:  $R^2 = 0.98$ ; LVM:  $R^2 = 0.97$ ; LS:  $R^2 = 0.87$ , CS:  $R^2 = 0.80$ ; in vivo: SV:  $R^2 = 0.92$ ; LVM:  $R^2 = 0.98$ ; LS: in vivo:  $R^2 = 0.84$ ; CS: in vivo:  $R^2 = 0.76$ ; all  $P < 0.05$ ). CONCLUSIONS: RT3DE is capable of quantifying the SV, LVM, and myocardial strain of fetal-sized hearts under different conditions. This nongated RT3DE may aid the evaluation of fetal cardiac function, providing a superior understanding of the progress of fetal heart disorders.

Zhu, T. C., Kim, M. M., Jacques, S. L., Penjweini, R., Dimofte, A., Finlay, J. C., et al. (2015). Real-time treatment light dose guidance of Pleural PDT: An update. *Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy XXIV*, , 9308.

The goal of this study was to develop and improve an infrared (IR) navigation system to deliver light dose uniformly during intracavitary PDT by tracking the movement of the light source and providing real-time feedback on the light fluence rate on the entire cavity surface area. In the current intrapleural PDT protocol, several detectors placed in selected locations in the pleural cavity monitor the light doses. To improve the delivery of light dose uniformity, an IR camera system is used to track the motion of the light source as well as the surface contour of the pleural cavity. Monte-Carlo simulation is used to improve the calculation algorithm for the effect of light that undergoes multiple scattering along the surface in addition to an improvement of the direct light calculation using an improved model that accounts for the anisotropy of the light from the light source. © 2015 SPIE.

Zimmerman, R. F., Belanger, E. S., & Pfeiffer, C. D. (2015). Skin infections in returned travelers: An update. *Current Infectious Disease Reports*, 17(3), 467-015-0467-8.

Dermatologic manifestations of travel-related illness are particularly vexing due to the broad differential diagnosis and clinicians' unfamiliarity with uncommonly seen diseases. This paper aims to educate and update the reader on selected infectious diseases in the returned traveler whose disease manifestations are primarily dermatologic. First, the evolving epidemiology of these infections is examined; understanding the geographic distribution of infectious etiologies helps refine and narrow the differential diagnosis. This is followed by a discussion of six important clinical syndromes including cutaneous larva migrans (CLM), cutaneous leishmaniasis, tungiasis, myiasis, antibiotic-resistant skin and soft tissue infection, and selected infections associated with fever and rash (e.g., measles, chikungunya virus infection, dengue fever, rickettsial spotted fevers). Familiarity with these syndromes and a situational awareness of their epidemiology will facilitate a prompt, accurate diagnosis and lead to appropriate treatment and prevention of further disease spread.

Zug, K. A., Pham, A. K., Belsito, D. V., Dekoven, J. G., DeLeo, V. A., Fowler, J. F., Jr., et al. (2014).

Patch testing in children from 2005 to 2012: Results from the north american contact dermatitis group. *Dermatitis*, 25(6), 345-355.

Background: Allergic contact dermatitis is common in children. Epicutaneous patch testing is an important tool for identifying responsible allergens. Objective: The objective of this study was to provide the patch test results from children (aged  $\leq 18$  years) examined by the North American Contact Dermatitis Group from 2005 to 2012. Methods: This is a retrospective analysis of children patch-tested with the North American Contact Dermatitis Group 65- or 70-allergen series. Frequencies and counts were compared with previously published data (2001-2004) using  $\chi^2$  statistics. Conclusions: A total of 883 children were tested during the study period. A percentage of 62.3% had  $\geq 1$  positive patch test and 56.7% had  $\geq 1$  relevant positive patch test. Frequencies of positive patch test and relevant positive patch test reaction were highest with nickel sulfate (28.1/25.6), cobalt chloride (12.3/9.1), neomycin sulfate (7.1/6.6), balsam of Peru (5.7/5.5), and lanolin alcohol 50% petrolatum vehicle (5.5/5.1). The  $>1$  positive patch test and Q1 relevant positive patch test in the children did not differ significantly from adults ( $\geq 19$  years) or from previously tested children (2001-2004). The percentage of clinically relevant positive patch tests for 27 allergens differed significantly between the children and adults. A total of 23.6% of children had a relevant positive reaction to at least 1 supplemental allergen. Differences in positive patch test and relevant positive patch test frequencies between children and adults as well as test periods confirm the importance of reporting periodic updates of patch testing in children to enhance clinicians' vigilance to clinically important allergens. © 2014 American Contact Dermatitis Society. All Rights Reserved.