References

Adams, J. R., & Bedrick, S. (2015). In Juan E.S., et al(Eds.), *Automatic indexing of journal abstracts with latent semantic analysis* Springer Verlag.

The BioASQ "Task on Large-Scale Online Biomedical Semantic Indexing" charges participants with assigning semantic tags to biomedical journal abstracts. We present a system that takes as input a biomedical abstract and uses latent semantic analysis to identify similar documents in the MEDLINE database. The system then uses a novel ranking scheme to select a list of MeSH tags from candidates drawn from the most similar documents. Our approach achieved better than baseline performance in both precision and recall. We suggest several possible strategies to improve the system's performance. © Springer International Publishing Switzerland 2015.

Aggarwal, S., Kusano, A. S., Carter, J. N., Gable, L., Thomas, C. R.,Jr, & Chang, D. T. (2015). Stress and burnout among residency program directors in united states radiation oncology programs. *International Journal of Radiation Oncology, Biology, Physics, 93*(4), 746-753.

PURPOSE: To evaluate stressors among radiation oncology residency program directors (PDs) and determine the prevalence and indicators of burnout. METHODS AND MATERIALS: An anonymous, online, cross-sectional survey was offered to PDs of US radiation oncology programs in the fall of 2014. Survey content examined individual and program demographics, perceptions surrounding the role of PD, and commonly encountered stressors. Burnout was assessed using the validated Maslach Burnout Inventory-Human Services Survey. RESULTS: In total, 47 of 88 PDs (53%) responded to the survey. Although 78% of respondents reported feeling "satisfied" or "highly satisfied" with their current role, 85% planned to remain as PD for <5 years. The most commonly cited stressors were satisfying Accreditation Council for Graduate Medical Education/Residency Review Committee requirements (47%), administrative duties (30%) and resident morale (28%). Three-quarters of respondents were satisfied that they became PDs. Overall, 11% of respondents met criteria for low burnout, 83% for moderate burnout, and 6% for high burnout. Not having served as a PD at a prior institution correlated with high depersonalization (OR 6.75, P=.04) and overall burnout (odds ratio [OR], 15.6; P=.04). Having more years on faculty prior to becoming PD correlated with less emotional exhaustion (OR, 0.44, P=.05) and depersonalization (OR, 0.20, P=.04). Finally, having dedicated time for PD duties

correlated with less emotional exhaustion (OR, 0.27, P=.04). CONCLUSIONS: Moderate levels of burnout are common in U.S. radiation oncology PDs with regulatory stressors being common. Despite this, many PDs are fulfilled with their role. Longitudinal studies assessing dynamic external factors and their influence on PD burnout would be beneficial.

Ahluwalia, S. C., Bekelman, D. B., Huynh, A. K., Prendergast, T. J., Shreve, S., & Lorenz, K. A. (2015). Barriers and strategies to an iterative model of advance care planning communication. *American Journal of Hospice and Palliative Medicine, 32*(8), 817-823.
Background: Early and repeated patient–provider conversations about advance care planning (ACP) are now widely recommended. We sought to characterize barriers and strategies for realizing an iterative model of ACP patient–provider communication. Methods: A total of 2 multidisciplinary focus groups and 3 semistructured interviews with 20 providers at a large Veterans Affairs medical center. Thematic analysis was employed to identify salient themes. Results: Barriers included variation among providers in approaches to ACP, lack of useful information about patient values to guide decision making, and ineffective communication between providers across settings. Strategies included eliciting patient values rather than specific treatment choices and an increased role for primary care in the ACP process. Conclusions: Greater attention to connecting providers across the continuum, maximizing the potential of the electronic health record, and linking patient experiences to their values may help to connect ACP communication across the continuum. © 2014, The Author(s) 2014.

Aicher, S. A., Hermes, S. M., & Hegarty, D. M. (2015). Denervation of the lacrimal gland leads to corneal hypoalgesia in a novel rat model of aqueous dry eye disease. *Investigative Ophthalmology and Visual Science, 56*(11), 6981-6989.
PURPOSE. Some dry eye disease (DED) patients have sensitized responses to corneal stimulation, while others experience hypoalgesia. Many patients have normal tear production, suggesting that reduced tears are not always the cause of DED sensory dysfunction. In this study, we show that disruption of lacrimal innervation can produce hypoalgesia without changing basal tear production. METHODS. Injection of a saporin toxin conjugate into the extraorbital lacrimal gland of male Sprague-Dawley rats was used to disrupt cholinergic innervation to the gland. Tear

production was assessed by phenol thread test. Corneal sensory responses to noxious stimuli were assessed using eye wipe behavior. Saporin DED animals were compared to animals treated with atropine to produce aqueous DED. RESULTS. Cholinergic innervation and acetylcholine content of the lacrimal gland were significantly reduced in saporin DED animals, yet basal tear production was normal. Saporin DED animals demonstrated normal eye wipe responses to corneal application of capsaicin, but showed hypoalgesia to corneal menthol. Corneal nerve fiber density was normal in saporin DED animals. Atropine-treated animals had reduced tear production but normal responses to ocular stimuli. CONCLUSIONS. Because only menthol responses were impaired, cold-sensitive corneal afferents appear to be selectively altered in our saporin DED model. Hypoalgesia is not due to reduced tear production, since we did not observe hypoalgesia in an atropine DED model. Corneal fiber density is unaltered in saporin DED animals, suggesting that molecular mechanisms of nociceptive signaling may be impaired. The saporin DED model will be useful for exploring the mechanism underlying corneal hypoalgesia. © 2015 The Association for Research in Vision and Ophthalmology, Inc.

Allen, A. R., Raber, J., Chakraborti, A., Sharma, S., & Fike, J. R. (2015). Fe irradiation alters spine density and dendritic complexity in the mouse hippocampus. *Radiation Research,*
A unique feature of the space radiation environment is the presence of high-energy charged particles, which can be significantly hazardous to space flight crews who are exposed during a mission. Health risks associated with high-LET radiation exposure include cognitive injury. The pathogenesis of this injury is unknown but may involve modifications to dendritic structure and/or alterations in dendritic spine density and morphology. In this study, 24 two-month-old C57BL6/J male mice were either whole-body irradiated with 0.5 Gy ^{56}Fe (600 MeV/n; n = 12) or sham irradiated (n = 12). Three months postirradiation animals were tested for locomotor activity and habituation. After behavioral testing, animals were euthanized and the brains were flash frozen. Compared to sham-irradiated mice, irradiated mice moved less when first introduced to the environment, although they did recognize the environment when re-exposed to it one day later. Exposure to ^{56}Fe radiation significantly compromised the dendritic architecture and reduced spine density throughout the hippocampal tri-synaptic network. To our knowledge, this

data represents the first reported evidence that high-LET radiation has deleterious effects on mature neurons associated with hippocampal learning and memory.

Allen, D. B., Backeljauw, P., Bidlingmaier, M., Biller, B., Boguszewski, M., Burman, P., et al. (2015). Growth hormone safety workshop position paper: A critical appraisal of recombinant human growth hormone therapy in children and adults. *European Journal of Endocrinology / European Federation of Endocrine Societies,*
Recombinant human growth hormone (rhGH) has been in use for 30 years, and over that time its safety and efficacy in children and adults has been subject to considerable scrutiny. In 2001, a statement from the GH Research Society (GRS) concluded that 'for approved indications, GH is safe'; however, the statement highlighted a number of areas for on-going surveillance of long-term safety including; cancer risk, impact on glucose homeostasis and use of high dose pharmacological rhGH treatment. Over the intervening years, there have been a number of publications addressing the safety of rhGH with regard to mortality, cancer and cardiovascular risk and the need for longterm surveillance of the increasing number of adults who were treated with rhGH in childhood. Against this backdrop of interest in safety, the European Society of Paediatric Endocrinology (ESPE), the GRS and the Pediatric Endocrine Society (PES) convened a meeting to reappraise the safety of rhGH. The ouput of the meeting is a concise position statement.

Alvarado, J. A., Chau, P., Wu, J., Juster, R., Shifera, A. S., & Geske, M. (2015). Profiling of cytokines secreted by conventional aqueous outflow pathway endothelial cells activated in vitro and ex vivo with laser irradiation. *Investigative Ophthalmology & Visual Science, 56*(12), 7100-7108.
PURPOSE: To profile which cytokine genes are differentially expressed (DE) as up- or downregulated by cultured human trabecular meshwork (TMEs) and Schlemm's canal endothelial cells (SCEs) after three experimental treatments consisting of selective laser trabeculoplasty (SLT) irradiation, exposure to media conditioned either by SLT-irradiated TMEs (TME-cm) or by SCEs (SCE-cm). Also, to profile which cytokines are upregulated ex vivo in SLT-irradiated human conventional aqueous outflow pathway (CAOP) tissues. METHODS: After each treatment, Affymetrix microarray assays were used to detect upregulated and downregulated genes for

cytokines and their receptors in TMEs and SCEs. ELISA and protein antibody arrays were used to detect upregulated cytokines secreted in SLT-irradiated CAOP tissues ex vivo. RESULTS: The SLT irradiation upregulated numerous cytokine genes in TMEs, but only a few in SCEs. Exposure to TME- and SCE-cm induced SCEs to upregulate many more cytokine genes than TMEs. Selective laser trabeculoplasty irradiation and exposure to TME-cm downregulated several cytokine genes in TMEs but none in SCEs. Selective laser trabeculoplasty irradiation induced one upregulated and three downregulated cytokine-receptor genes in TMEs but none in SCEs. Exposure to TME-cm induced upregulation of one and downregulation of another receptor gene in TMEs, whereas two unique cytokine-receptor genes were upregulated in SCEs. Cytokine protein expression analysis showed that at least eight cytokines were upregulated in SLT-irradiated human CAOP tissues in situ/ex vivo. CONCLUSIONS: This study has helped us identify a cytokine signaling pathway and to consider newly identified mechanisms regulating aqueous outflow that may lay the foundation for the future development of cytokine-based glaucoma therapies.

Anagnostou, M., Mountouris, G., Silikas, N., Kletsas, D., & Eliades, G. (2015). Chemical, mechanical and biological properties of contemporary composite surface sealers. *Dental Materials : Official Publication of the Academy of Dental Materials,*

OBJECTIVES: To evaluate the chemical, mechanical, and biological properties of modern composite surface sealers (CSS) having different compositions. METHODS: The CSS products tested were Biscover LV (BC), Durafinish (DF), G-Coat Plus (GC), and Permaseal (PS). The tests performed were: (A): degree of conversion (DC%) by ATR-FTIR spectroscopy; (B): thickness of O_2-inhibition layer by transmission optical microscopy; (C): surface hardness, 10min after irradiation and following 1 week water storage, employing a Vickers indenter (VHN); (D): color (DeltaE*) and gloss changes (DeltaGU) after toothbrush abrasion, using L*a*b* colorimetry and glossimetry; (E): accelerated wear (GC,PS only) by an OHSU wear simulator plus 3D profilometric analysis, and (F): cytotoxicity testing of aqueous CSS eluents on human gingival fibroblast cultures employing the methyl-3H thymidine DNA labeling method. Statistical analyses included 1-way (A, B, DeltaE*, DeltaGU) and 2-way (C, F) ANOVAs, plus Tukey post hoc tests. Student's t-test was used to evaluate the results of the accelerated wear test (alpha=0.05 for all). RESULTS: The rankings of the statistical significant differences were: (A) PS

(64.9)>DF,BC,GC (56.1-53.9) DC%; (B) DF,PS (12.3,9.8)>GC,BC (5.2,4.8) mum; (C): GC (37.6)>BC,DF (32.6,31.1)>PS (26.6) VHN (10min/dry) and BC,DF (29.3,28.7)>GC(26.5)>PS(21.6) VHN (1w/water), with no significant material/storage condition interaction; (D): no differences were found among GC,DF,BC,PS (0.67-1.11) DeltaE*, with all values within the visually acceptable range and PS,BC (32.8,29.4)>GC,DF (19.4,12.9) DeltaGU; (E): no differences were found between GC and PS in volume loss (0.10,0.11mm3), maximum (113.9,130.5mum) and mean wear depths (30.3,27.5mum); (F): at 1% v/v concentration, DF showed toxicity (23% vital cells vs 95-102% for others). However, at 5% v/v concentration DF (0%) and BC (9%) were the most toxic, whereas GC (58%) and PS (56%) showed moderate toxicity. SIGNIFICANCE: Important chemical, mechanical, and biological properties exist among the CSS tested, which may affect their clinical performance.

Arora, A., Schwarz, E., & Blinkhorn, A. S. (2011). Risk factors for early childhood caries in disadvantaged populations. *Journal of Investigative and Clinical Dentistry, 2*(4), 223-228. Early childhood caries is a significant international public health problem. The aim of this paper was to review the current evidence of the risk factors for dental caries in disadvantaged children under 6 years of age. Medline, Cochrane, and PubMed database searches were conducted. Systematic reviews were used where available, or meta-analyses; randomized, controlled trials; and cohort, case-control, and cross-sectional studies (in that order). Studies were restricted to those published in English from 1990 to October 2010. Early childhood caries has a complex etiology with biological, behavioral, and sociodemographic influences. Evidence suggests that young children are most likely to develop caries if Streptococcus mutans is acquired at an early age, although this is influenced by other factors, such as oral hygiene, fluoride, diet, dental visit patterns, socioeconomic status, ethnicity, and health literacy. Etiological pathways should be taken into consideration when designing interventions to prevent dental caries in disadvantaged preschool children.

Aslam, M. F., Osmundsen, B., Edwards, S. R., Matthews, C., & Gregory, W. T. (2015). Preoperative prolapse stage as predictor of failure of sacrocolpopexy. *Female Pelvic Medicine & Reconstructive Surgery,*

OBJECTIVES: Our aim was to determine if there was a correlation between the preoperative prolapse stage and postoperative recurrence of prolapse 1 year after sacrocolpopexy. Our null hypothesis is that the preoperative stage of prolapse does not increase the risk of recurrence. METHODS: This is a multicenter cohort study from 3 centers. We included subjects who underwent robotic-assisted sacrocolpopexy and completed a standardized 1-year follow-up from 2009-2014. All subjects underwent a complete preoperative evaluation and completed 12 months of follow-up with the pelvic organ prolapse quantification examination. We compared those subjects who met the definition of recurrence with those who did not, analyzing the following covariates: stage of prolapse using International Continence Society (ICS) definitions, individual pelvic organ prolapse quantification points, age, body mass index, race, exogenous estrogen use, menopause, smoking, vaginal parity, cesarean section, and performance of concomitant procedures. We defined recurrence as any prolapse beyond the hymen. RESULTS: We had 125 women from 3 centers who met our criteria, with 23.2% of them having recurrence at 1 year. We found that recurrence increased as the preoperative ICS stage of prolapse increased (P = <0.001 in the univariate model). In the multivariate model, using logistic regression, we found that the risk of recurrence of pelvic organ prolapse increased as the presurgery clinical stage increased with an odds ratio of 3.8 (95% confidence interval, 1.5-9) when controlling for age, menopausal status, and genital hiatus (P = 0.004). CONCLUSIONS: Much like a higher stage of disease in oncology, we found that increasing stage of prolapse preoperatively increased the risk of recurrence at 1 year after sacrocolpopexy.

Aziz, M. F., Abrons, R. O., Cattano, D., Bayman, E. O., Swanson, D. E., Hagberg, C. A., et al. (2015). First-attempt intubation success of video laryngoscopy in patients with anticipated difficult direct laryngoscopy: A multicenter randomized controlled trial comparing the C-MAC D-blade versus the GlideScope in a mixed provider and diverse patient population. *Anesthesia and Analgesia,* BACKGROUND: Intubation success in patients with predicted difficult airways is improved by video laryngoscopy. In particular, acute-angle video laryngoscopes are now frequently chosen for endotracheal intubation in these patients. However, there is no evidence concerning whether different acute-angle video laryngoscopes can be used interchangeably in this scenario and would allow endotracheal intubation with the same success rate. We therefore tested whether first-

attempt intubation success is similar when using a newly introduced acute-angle blade, that is an element of an extended airway management system (C-MAC D-Blade) compared with a well-established acute-angle video laryngoscope (GlideScope). METHODS: In this large multicentered prospective randomized controlled noninferiority trial, patients requiring general anesthesia for elective surgery and presenting with clinical predictors of difficult laryngoscopy were randomly assigned to intubation using either the C-MAC D-Blade or the GlideScope video laryngoscope. The hypothesis was that first-attempt intubation success using the new device (D-Blade) is no >4% less than the established device (GlideScope), which would determine noninferiority of the new instrument versus the established instrument. The secondary outcomes we observed included intubation success with multiple attempts and airway-related complications within 7 days of enrollment. RESULTS: Eleven hundred patients were randomly assigned to either video laryngoscope. Intubation success rate on first attempt was 96.2% in the GlideScope group and 93.4% in the C-MAC D-Blade group. Although the absolute difference between the 2 groups was only 2.8%, the 90.35% upper confidence limit of the difference exceeded the predefined margin (4.98%), indicating a rejection of the noninferiority hypothesis for first-attempt intubation success. For attending anesthesiologists, and upon multiple attempts, intubation success did not differ between systems. Pharyngeal injury was noted in 1% of the patients, and the incidence did not differ between interventional groups. CONCLUSIONS: Head-to-head comparison in this large multicenter trial revealed that the newly introduced C-MAC D-Blade does not yield the same first-attempt intubation success as the GlideScope in patients with predicted difficult laryngoscopy except in the hands of attending anesthesiologists. Additional research would be necessary to identify potential causes for this difference. Intubation success rates were very high with both systems, indicating that acute-angle video laryngoscopy is an exceptionally successful strategy for the initial approach to endotracheal intubation in patients with predicted difficult laryngoscopy.

Baptista, A. M., Seaton, C., Wilkin, M. P., Riseman, S. F., Needoba, J. A., Maier, D., et al. (2015). Infrastructure for collaborative science and societal applications in the columbia river estuary. *Frontiers of Earth Science, 9*(4), 659-682.

To meet societal needs, modern estuarine science needs to be interdisciplinary and collaborative,

combine discovery with hypotheses testing, and be responsive to issues facing both regional and global stakeholders. Such an approach is best conducted with the benefit of data-rich environments, where information from sensors and models is openly accessible within convenient timeframes. Here, we introduce the operational infrastructure of one such data-rich environment, a collaboratory created to support (a) interdisciplinary research in the Columbia River estuary by the multi-institutional team of investigators of the Science and Technology Center for Coastal Margin Observation & Prediction and (b) the integration of scientific knowledge into regional decision making. Core components of the operational infrastructure are an observation network, a modeling system and a cyber-infrastructure, each of which is described. The observation network is anchored on an extensive array of long-term stations, many of them interdisciplinary, and is complemented by on-demand deployment of temporary stations and mobile platforms, often in coordinated field campaigns. The modeling system is based on finiteelement unstructured-grid codes and includes operational and process-oriented simulations of circulation, sediments and ecosystem processes. The flow of information is managed through a dedicated cyber-infrastructure, conversant with regional and national observing systems. © 2015, Higher Education Press and Springer-Verlag Berlin Heidelberg.

Barabaschi, G. D., Manoharan, V., Li, Q., & Bertassoni, L. E. (2015). Engineering pre-vascularized scaffolds for bone regeneration. *Advances in Experimental Medicine and Biology, 881*, 79-94. Survival of functional tissue constructs of clinically relevant size depends on the formation of an organized and uniformly distributed network of blood vessels and capillaries. The lack of such vasculature leads to spatio-temporal gradients in oxygen, nutrients and accumulation of waste products inside engineered tissue constructs resulting in negative biological events at the core of the scaffold. Unavailability of a well-defined vasculature also results in ineffective integration of scaffolds to the host vasculature upon implantation. Arguably, one of the greatest challenges in engineering clinically relevant bone substitutes, therefore, has been the development of vascularized bone scaffolds. Various approaches ranging from peptide and growth factor functionalized biomaterials to hyper-porous scaffolds have been proposed to address this problem with reasonable success. An emerging alternative to address this challenge has been the fabrication of pre-vascularized scaffolds by taking advantage of biomanufacturing techniques,

such as soft- and photo-lithography or 3D bioprinting, and cell-based approaches, where functional capillaries are engineered in cell-laden scaffolds prior to implantation. These strategies seek to engineer pre-vascularized tissues in vitro, allowing for improved anastomosis with the host vasculature upon implantation, while also improving cell viability and tissue development in vitro. This book chapter provides an overview of recent methods to engineer pre-vascularized scaffolds for bone regeneration. We first review the development of functional blood capillaries in bony structures and discuss controlled delivery of growth factors, co-culture systems, and on-chip studies to engineer vascularized cell-laden biomaterials. Lastly, we review recent studies using microfabrication techniques and 3D printing to engineer pre-vascularized scaffolds for bone tissue engineering.

Basta, A. M., Lusk, L. A., Keller, R. L., & Filly, R. A. (2015). Fetal stomach position predicts neonatal outcomes in isolated left-sided congenital diaphragmatic hernia. *Fetal Diagnosis and Therapy,* INTRODUCTION: We sought to determine the relationship between the degree of stomach herniation by antenatal sonography and neonatal outcomes in fetuses with isolated left-sided congenital diaphragmatic hernia (CDH). MATERIALS AND METHODS: We retrospectively reviewed neonatal medical records and antenatal sonography of fetuses with isolated left CDH cared for at a single institution (2000-2012). Fetal stomach position was classified on sonography as follows: intra-abdominal, anterior left chest, mid-to-posterior left chest, or retrocardiac (right chest). RESULTS: Ninety fetuses were included with 70% surviving to neonatal discharge. Stomach position was intra-abdominal in 14% (n = 13), anterior left chest in 19% (n = 17), mid-to-posterior left chest in 41% (n = 37), and retrocardiac in 26% (n = 23). Increasingly abnormal stomach position was linearly associated with an increased odds of death (OR 4.8, 95% CI 2.1-10.9), extracorporeal membrane oxygenation (ECMO; OR 5.6, 95% CI 1.9-16.7), nonprimary diaphragmatic repair (OR 2.7, 95% CI 1.4-5.5), prolonged mechanical ventilation (OR 5.9, 95% CI 2.3-15.6), and prolonged respiratory support (OR 4.0, 95% CI 1.6-9.9). All fetuses with intra-abdominal stomach position survived without substantial respiratory morbidity or need for ECMO. DISCUSSION: Fetal stomach position is strongly associated with neonatal outcomes in isolated left CDH. This objective tool may allow for accurate prognostication in a variety of clinical settings.

Bayestehtashk, A., & Shafran, I. (2015). Efficient and accurate multivariate class conditional densities using copula. *40th IEEE International Conference on Acoustics, Speech, and Signal Processing, ICASSP 2015, , 2015-August.* pp. 3936-3940.

Univariate densities can be modeled accurately and efficiently using nonparametric kernel density estimators, which unfortunately cannot be easily extended to the multivariate case. As an alternative, Gaussian mixture model is used to approximate underlying multivariate distributions, especially because its estimation is relatively straight forward through EM algorithm. However, the multivariate Gaussian mixture model imposes a particular form on the marginal, a Gaussian mixture model. This is a strong assumption on the marginal and is violated in many practical applications. We propose a simple generative classification model based on the copula model that takes advantage of the accuracy of the nonparametric univariate density estimator and the multivariate dependencies captured in the Gaussian mixture model, thus alleviating the aforementioned limitations. We compare the performance of our models with previous classification benchmarks from UCI repository and show that for the same number of parameters the proposed models consistently outperforms Gaussian mixture models. We find that these generative models perform as well or better than Support Vector Machine (SVM). © 2015 IEEE.

Bernardi, P., & Forte, M. (2015). Commentary: SPG7 is an essential and conserved component of the mitochondrial permeability transition pore. *Frontiers in Physiology, 6*, 320.

Blanke, C. D., Rankin, C., Corless, C., Eary, J. F., Mulder, K., Okuno, S. H., et al. (2015). S0502: A SWOG phase III randomized study of imatinib, with or without bevacizumab, in patients with untreated metastatic or unresectable gastrointestinal stromal tumors. *The Oncologist,* LESSONS LEARNED: Despite having significant rationale, S0502 failed to accrue for a number of reasons.Vetting a trial first, with scientific experts and funding agencies, does not guarantee success, especially when dealing with a rare tumor and/or one with an existing highly effective therapy.In the present case, adding an intravenous drug to an oral medication as part of a regimen expected to be continued for many years likely decreased patient (and physician) convenience and, thus, interest in the study. BACKGROUND: Imatinib mesylate, a potent inhibitor of the KIT and PDGFR tyrosine kinases, is highly effective in the treatment of advanced

gastrointestinal stromal tumors (GISTs). However, most imatinib-treated tumors eventually become resistant, accounting for a median progression-free survival of 19-23 months. Expression of vascular endothelial growth factor (VEGF) correlates with poor prognosis in GIST; bevacizumab, a monoclonal antibody against VEGF, is effective in a variety of solid tumors. We postulated combination therapy with imatinib plus bevacizumab would benefit patients with advanced GIST, particularly those reliant on VEGFA-dependent angiogenesis. METHODS: Patients with metastatic or surgically unresectable GIST were eligible for this phase III open-label clinical trial, S0502. At registration, patients were randomly assigned to either imatinib 400 mg (standard) or 800 mg (patients with exon 9 KIT mutations), or imatinib plus bevacizumab, 7.5 mg/kg i.v. every 3 weeks. Patients were treated to progression, symptomatic deterioration, unacceptable toxicity, treatment delay greater than 4 weeks, or patient choice to withdraw from the study. The primary objective was to determine whether the addition of bevacizumab to imatinib would improve progression-free survival (PFS) in first-line treatment of incurable GIST. RESULTS: S0502 opened on April 15, 2008. As of fall 2009, only 12 patients from at least 178 eligible SWOG centers plus those participating through Cancer Trials Support Unit had been entered in the study. Despite an aggressive promotion scheme involving the other cooperative groups and a major GIST patient advocacy group, accrual remained slow. The trial was closed on October 1, 2009, having accrued only 2% of the 572 patients planned. No scientific conclusions were forthcoming because of the small number of patients entered in the study. Two patients of the 6 in the combination arm reported grade 3 toxicities, 1 with proteinuria and 1 with fatigue, upper gastrointestinal hemorrhage, and anemia. CONCLUSION: No conclusions may be drawn from this trial and, thus, the combination of imatinib plus bevacizumab cannot be recommended for use.

Bleyer, A., Baines, C., & Miller, A. B. (2015). Impact of screening mammography on breast cancer mortality. *International Journal of Cancer.Journal International Du Cancer,*
The degree to which observed reductions in breast cancer mortality is attributable to screening mammography has become increasingly controversial. We examined this issue with three fundamentally different approaches: 1) Chronology - the temporal relationship of the onset of breast cancer mortality 1551decline and the national implementation of screening

mammography; 2) Magnitude - the degree to which breast cancer mortality declined relative to the amount (penetration) of screening mammography; 3) Analogy - the pattern of mortality rate reductions of other cancers for which population screening is not conducted. Chronology and magnitude were assessed with data from Europe and North America, with three methods applied to magnitude. A comparison of eight countries in Europe and North America does not demonstrate a correlation between the penetration of national screening and either the chronology or magnitude of national breast cancer mortality reduction. In the United States, the magnitude of the mortality decline is greater in the unscreened, younger women than in the screened population and regional variation in the rate of breast cancer mortality reduction is not correlated with screening penetrance, either as self-reported or by the magnitude of screening-induced increase in early-stage disease. Analogy analysis of United States data identifies 14 other cancers with a similar distinct onset of mortality reduction for which screening is not performed. These five lines of evidence from three different approaches and additional observations discussed do not support the hypothesis that mammography screening is a primary reason for the breast cancer mortality reduction in Europe and North America.

Bobeck, E. N., Ingram, S. L., Hermes, S. M., Aicher, S. A., & Morgan, M. M. (2016). Ligand-biased activation of extracellular signal-regulated kinase 1/2 leads to differences in opioid induced antinociception and tolerance. *Behavioural Brain Research, 298*, 17-24.
Opioids produce antinociception by activation of G protein signaling linked to the mu-opioid receptor (MOPr). However, opioid binding to the MOPr also activates β-arrestin signaling. Opioids such as DAMGO and fentanyl differ in their relative efficacy for activation of these signaling cascades, but the behavioral consequences of this differential signaling are not known. The purpose of this study was to evaluate the behavioral significance of G protein and internalization dependent signaling within ventrolateral periaqueductal gray (vlPAG). Antinociception induced by microinjecting DAMGO into the vlPAG was attenuated by blocking Gαi/o protein signaling with administration of pertussis toxin (PTX), preventing internalization with administration of dynamin dominant-negative inhibitory peptide (dyn-DN) or direct inhibition of ERK1/2 with administration of the MEK inhibitor, U0126. In contrast, the antinociceptive effect of microinjecting fentanyl into

the vlPAG was not altered by administration of PTX or U0126, and was enhanced by administration of dyn-DN. Microinjection of DAMGO, but not fentanyl, into the vlPAG induced phosphorylation of ERK1/2, which was blocked by inhibiting receptor internalization with administration of dyn-DN, but not by inhibition of Gαi/o proteins. ERK1/2 inhibition also prevented the development and expression of tolerance to repeated DAMGO microinjections, but had no effect on fentanyl tolerance. These data reveal that ERK1/2 activation following MOPr internalization contributes to the antinociceptive effect of some (e.g., DAMGO), but not all opioids (e.g., fentanyl) despite the known similarities for these agonists to induce β-arrestin recruitment and internalization. © 2015 Elsevier B.V.

Bone, W. P., Washington, N. L., Buske, O. J., Adams, D. R., Davis, J., Draper, D., et al. (2015). Computational evaluation of exome sequence data using human and model organism phenotypes improves diagnostic efficiency. *Genetics in Medicine : Official Journal of the American College of Medical Genetics,*

PURPOSE: Medical diagnosis and molecular or biochemical confirmation typically rely on the knowledge of the clinician. Although this is very difficult in extremely rare diseases, we hypothesized that the recording of patient phenotypes in Human Phenotype Ontology (HPO) terms and computationally ranking putative disease-associated sequence variants improves diagnosis, particularly for patients with atypical clinical profiles. METHODS: Using simulated exomes and the National Institutes of Health Undiagnosed Diseases Program (UDP) patient cohort and associated exome sequence, we tested our hypothesis using Exomiser. Exomiser ranks candidate variants based on patient phenotype similarity to (i) known disease-gene phenotypes, (ii) model organism phenotypes of candidate orthologs, and (iii) phenotypes of protein-protein association neighbors. RESULTS: Benchmarking showed Exomiser ranked the causal variant as the top hit in 97% of known disease-gene associations and ranked the correct seeded variant in up to 87% when detectable disease-gene associations were unavailable. Using UDP data, Exomiser ranked the causative variant(s) within the top 10 variants for 11 previously diagnosed variants and achieved a diagnosis for 4 of 23 cases undiagnosed by clinical evaluation. CONCLUSION: Structured phenotyping of patients and computational analysis are effective

adjuncts for diagnosing patients with genetic disorders.Genet Med advance online publication 12 November 2015Genetics in Medicine (2015); doi:10.1038/gim.2015.137.

Boone-Heinonen, J., Messer, L. C., Fortmann, S. P., Wallack, L., & Thornburg, K. L. (2015). From fatalism to mitigation: A conceptual framework for mitigating fetal programming of chronic disease by maternal obesity. *Preventive Medicine, 81*, 451-459.

Prenatal development is recognized as a critical period in the etiology of obesity and cardiometabolic disease. Potential strategies to reduce maternal obesity-induced risk later in life have been largely overlooked. In this paper, we first propose a conceptual framework for the role of public health and preventive medicine in mitigating the effects of fetal programming. Second, we review a small but growing body of research (through August 2015) that examines interactive effects of maternal obesity and two public health foci - diet and physical activity - in the offspring. Results of the review support the hypothesis that diet and physical activity after early life can attenuate disease susceptibility induced by maternal obesity, but human evidence is scant. Based on the review, we identify major gaps relevant for prevention research, such as characterizing the type and dose response of dietary and physical activity exposures that modify the adverse effects of maternal obesity in the offspring. Third, we discuss potential implications of interactions between maternal obesity and postnatal dietary and physical activity exposures for interventions to mitigate maternal obesity-induced risk among children. Our conceptual framework, evidence review, and future research directions offer a platform to develop, test, and implement fetal programming mitigation strategies for the current and future generations of children.

Bowler, R. M., & Lezak, M. D. (2015). Neuropsychologic evaluation and exposure to neurotoxicants. *Handbook of Clinical Neurology, 131*, 23-45.

The history of neuropsychologic assessment describes the development of a psychometric approach to neuropsychologic measurement, based on the initial clinical/theoretical approach exemplified by pioneers, who also discussed different brain functions and hypotheses for clinical exploration and treatment. Early neuropsychologic assessment practices in the USA arose out of the need to screen, diagnose, and treat World War II veterans who returned with brain injuries.

Clinical testing was used to determine treatment and rehabilitation potential. Clinical psychologists had previously developed educational tests to investigate students' abilities and disabilities. Using population studies, primarily in the USA, Canada and Europe, neuropsychologists developed standardized test scores, permitting comparisons of scores based on the normal curve and evolving knowledge of brain/behavior relationships. In clinical interpretations, neuropsychologists use extensive normative data based on cognitive, mood, executive, neurologic, and motor brain functions of groups with different cultural and educational backgrounds and psychiatric illnesses. Large groups of workers can be screened with a brief neuropsychologic screening test battery to assess the psychologic status of personnel. Commonly used tests by domain are described, as well as patterns of acute and chronic neurotoxicant exposures, treatment, and rehabilitation. Future developments will relate imaging studies to neuropsychologic performance.

Brady, T. M., Appel, L. J., Holmes, K. W., Fivush, B., & Miller, E. R.,3rd. (2015). Association between adiposity and left ventricular mass in children with hypertension. *Journal of Clinical Hypertension (Greenwich, Conn.),*

Left ventricular hypertrophy (LVH) is prevalent among hypertensive children; however, blood pressure (BP) does not predict its presence. The authors conducted a 1-year prospective cohort study to examine the hypothesis that obesity-related risk factors are associated with left ventricular mass index (LVMI) in hypertensive children, and the association between adiposity and LVMI is mediated by BP-dependent and -independent pathways. A total of 49 hypertensive children were enrolled: 51% were overweight/obese and 41% had LVH at baseline. Children overweight/obese at baseline and follow-up had a greater LVMI increase than those of healthy weight at each visit: mean change of 6.4 g/m2.7 vs 0.95 g/m2.7 . Baseline body mass index z score was independently associated with LVMI change (beta=4.08, 1.54-6.61; P=.002). Only pulse pressure and serum aldosterone partially mediated this relationship. Hypertensive youth manifest multiple cardiovascular disease risk factors that worsen over time despite treatment. Of these, adiposity is most associated with LVH and increasing LVMI.

Breen, H. (2015). Assessing online collaborative discourse. *Nursing Forum, 50*(4), 218-227.

Purpose: This qualitative study using transcript analysis was undertaken to clarify the value of Harasim's Online Collaborative Learning Theory as a way to assess the collaborative process within nursing education. The theory incorporated three phases: (a) idea generating; (b) idea organizing; and (c) intellectual convergence. Method: The transcripts of asynchronous discussions from a 2-week module about disaster nursing using a virtual community were analyzed and formed the data for this study. Findings: This study supports the use of Online Collaborative Learning Theory as a framework for assessing online collaborative discourse. Individual or group outcomes were required for the students to move through all three phases of the theory. Discussion/Conclusion: The phases of the Online Collaborative Learning Theory could be used to evaluate the student's ability to collaborate. It is recommended that group process skills, which have more to do with interpersonal skills, be evaluated separately from collaborative learning, which has more to do with cognitive skills. Both are required for practicing nurses. When evaluated separately, the student learning needs are more clearly delineated. © 2015 Wiley Periodicals, Inc.

Brown, S. A., Brumback, T., Tomlinson, K., Cummins, K., Thompson, W. K., Nagel, B. J., et al. (2015). The national consortium on alcohol and NeuroDevelopment in adolescence (NCANDA): A multisite study of adolescent development and substance use. *Journal of Studies on Alcohol and Drugs, 76*(6), 895-908.

OBJECTIVE: During adolescence, neurobiological maturation occurs concurrently with social and interpersonal changes, including the initiation of alcohol and other substance use. The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) is designed to disentangle the complex relationships between onset, escalation, and desistance of alcohol use and changes in neurocognitive functioning and neuromaturation. METHOD: A sample of 831 youth, ages 12-21 years, was recruited at five sites across the United States, oversampling those at risk for alcohol use problems. Most (83%) had limited or no history of alcohol or other drug use, and a smaller portion (17%) exceeded drinking thresholds. A comprehensive assessment of biological development, family background, psychiatric symptomatology, and neuropsychological functioning-in addition to anatomical, diffusion, and functional brain magnetic resonance imaging-

was completed at baseline. RESULTS: The NCANDA sample of youth is nationally representative of sex and racial/ethnic groups. More than 50% have at least one risk characteristic for subsequent heavy drinking (e.g., family history, internalizing or externalizing symptoms). As expected, those who exceeded drinking thresholds (n = 139) differ from those who did not (n = 692) on identified factors associated with early alcohol use and problems. CONCLUSIONS: NCANDA successfully recruited a large sample of adolescents and comprehensively assessed psychosocial functioning across multiple domains. Based on the sample's risk profile, NCANDA is well positioned to capture the transition into drinking and alcohol problems in a large portion of the cohort, as well as to help disentangle the associations between alcohol use, neurobiological maturation, and neurocognitive development and functioning.

Burfeind, K. G., Michaelis, K. A., & Marks, D. L. (2015). The central role of hypothalamic inflammation in the acute illness response and cachexia. *Seminars in Cell & Developmental Biology,* When challenged with a variety of inflammatory threats, multiple systems across the body undergo physiological responses to promote defense and survival. The constellation of fever, anorexia, and fatigue is known as the acute illness response, and represents an adaptive behavioral and physiological reaction to stimuli such as infection. On the other end of the spectrum, cachexia is a deadly and clinically challenging syndrome involving anorexia, fatigue, and muscle wasting. Both of these processes are governed by inflammatory mediators including cytokines, chemokines, and immune cells. Though the effects of cachexia can be partially explained by direct effects of disease processes on wasting tissues, a growing body of evidence shows the central nervous system (CNS) also plays an essential mechanistic role in cachexia. In the context of inflammatory stress, the hypothalamus integrates signals from peripheral systems, which it translates into neuroendocrine perturbations, altered neuronal signaling, and global metabolic derangements. Therefore, we will discuss how hypothalamic inflammation is an essential driver of both the acute illness response and cachexia, and why this organ is uniquely equipped to generate and maintain chronic inflammation. First, we will focus on the role of the hypothalamus in acute responses to dietary and infectious stimuli. Next, we will discuss the role of cytokines in driving homeostatic disequilibrium, resulting in muscle wasting, anorexia, and

weight loss. Finally, we will address mechanisms and mediators of chronic hypothalamic inflammation, including endothelial cells, chemokines, and peripheral leukocytes.

Buss, B. A., Schulz, L. T., Reed, K. D., & Fox, B. C. (2015). MALDI-TOF utility in a region with low antibacterial resistance rates. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America,*

Butler, M. P., Smales, C., Wu, H., Hussain, M. V., Mohamed, Y. A., Morimoto, M., et al. (2015). The circadian system contributes to apnea lengthening across the night in obstructive sleep apnea. *Sleep, 38*(11), 1793-1801.
Study Objective: To test the hypothesis that respiratory event duration exhibits an endogenous circadian rhythm. Design: Within-subject and between-subjects. Settings: Inpatient intensive physiologic monitoring unit at the Brigham and Women's Hospital. Participants: Seven subjects with moderate/severe sleep apnea and four controls, age 48 (SD = 12) years, 7 males. Interventions: Subjects completed a 5-day inpatient protocol in dim light. Polysomnography was recorded during an initial control 8-h night scheduled at the usual sleep time, then through 10 recurrent cycles of 2 h 40 min sleep and 2 h 40 min wake evenly distributed across all circadian phases, and finally during another 8-h control sleep period. Measurements and Results: Event durations, desaturations, and apnea-hypopnea index for each sleep opportunity were assessed according to circadian phase (derived from salivary melatonin), time into sleep, and sleep stage. Average respiratory event durations in NREM sleep significantly lengthened across both control nights (21.9 to 28.2 sec and 23.7 to 30.2 sec, respectively). During the circadian protocol, event duration in NREM increased across the circadian phases that corresponded to the usual sleep period, accounting for > 50% of the increase across normal 8-h control nights. AHI and desaturations were also rhythmic: AHI was highest in the biological day while desaturations were greatest in the biological night. Conclusions: The endogenous circadian system plays an important role in the prolongation of respiratory events across the night, and might provide a novel therapeutic target for modulating sleep apnea.

Calderwood, M. S., Vaz, L. E., Tse Kawai, A., Jin, R., Rett, M. D., Grant, P. S., et al. (2015). Impact of hospital operating margin on central line-associated bloodstream infections following medicare's

hospital-acquired conditions payment policy. *Infection Control and Hospital Epidemiology, ,* 1-4.

In October 2008, Medicare ceased additional payment for hospital-acquired conditions not present on admission. We evaluated the policy's differential impact in hospitals with high vs low operating margins. Medicare's payment policy may have had an impact on reducing central line-associated bloodstream infections in hospitals with low operating margins. Infect. Control Hosp. Epidemiol. 2015;00(0):1-4.

Campbell, B. K., Guydish, J., Le, T., Wells, E. A., & McCarty, D. (2015). The relationship of therapeutic alliance and treatment delivery fidelity with treatment retention in a multisite trial of twelve-step facilitation. *Psychology of Addictive Behaviors, 29*(1), 106-113.

This study examined associations of therapeutic alliance and treatment delivery fidelity with treatment retention in Stimulant Abusers to Engage in Twelve-Step (STAGE-12), a community-based trial of 12-Step Facilitation (TSF) conducted within the National Drug Abuse Treatment Clinical Trials Network (CTN). The STAGE-12 trial randomized 234 stimulant abusers enrolled in 10 outpatient drug treatment programs to an eight-session, group and individual TSF intervention. During the study, TSF participants rated therapeutic alliance using the Helping Alliance questionnaire-II. After the study, independent raters evaluated treatment delivery fidelity of all TSF sessions on adherence, competence, and therapist empathy. Poisson regression modeling examined relationships of treatment delivery fidelity and therapeutic alliance with treatment retention (measured by number of sessions attended) for 174 participants with complete fidelity and alliance data. Therapeutic alliance (p =.005) and therapist competence (p =.010) were significantly associated with better treatment retention. Therapist adherence was associated with poorer retention in a nonsignificant trend (p =.061). In conclusion, stronger therapeutic alliance and higher therapist competence in the delivery of a TSF intervention were associated with better treatment retention whereas treatment adherence was not. Training and fidelity monitoring of TSF should focus on general therapist skills and therapeutic alliance development to maximize treatment retention. © 2014 American Psychological Association.

Canales, B. K., Sinclair, L., Kang, D., Mench, A. M., Arreola, M., & Bird, V. G. (2015). Changing default fluoroscopy equipment settings decreases entrance skin dose in endourology patients. *The*

PURPOSE: Proper fluoroscopic education and protocols may reduce patient radiation dose, but few prospective studies in urology have been performed. Using optically-stimulated luminescent dosimeters (OSLDs), we tested if fluoroscopy time (FT) and/or entrance skin dose (ESD) would decrease after educational and radiation reduction protocols. MATERIALS AND METHODS: At default manufacturer settings, FT and ESD were prospectively measured using OSLDs on patients undergoing ureteroscopy (URS), retrograde pyelogram/stent (RPG), or percutaneous nephrolithotomy with access (PCNL) for stone disease. A validated radiation safety competency test was then administered to urology faculty and residents before and after web-based, hands-on fluoroscopy training. Default fluoroscopy settings were changed from continuous to intermittent pulse rate and from standard to half-dose output. FT and ESD were then recollected. RESULTS: Pre- (n=44) and post-protocol (n=50) stone patient cohorts were similarly matched. The change in mean FT and ESD from pre- to post-protocol was: -0.6 minutes (p=0.62) and -11.6 mGy (33%, p < 0.001) for PCNL; +0.5 minutes (p=0.42) and -0.1 mGy for URS (34%, p=0.31); +0.1 minutes (p=0.85) and -0.1 mGy (29%, p=0.49) for RPGs. Urologists' post-training test scores increased 30% (p=0.1) from pre-training. CONCLUSIONS: Radiation safety training protocols improved clinical knowledge but did not significantly alter FT. Changing equipment default settings to intermittent pulse rate (12 frames/sec) and half-dose lowered ESD by 30% across all endourology patients but most significantly during PCNL. To limit patient radiation exposure, fluoroscopy default settings should be decreased prior to all endourology procedures, and image equipment manufacturers should consider lowering their standard default renal settings.

Cannell, M. B., Weitlauf, J. C., Garcia, L., Andresen, E. M., Margolis, K. L., & Manini, T. M. (2015). Cross-sectional and longitudinal risk of physical impairment in a cohort of postmenopausal women who experience physical and verbal abuse. *BMC Women's Health, 15*(1), 98-015-0258-2.
BACKGROUND: Exposure to interpersonal violence, namely verbal and physical abuse, is a highly prevalent threat to women's health and well-being. Among older, post-menopausal women, several researchers have characterized a possible bi-directional relationship of abuse exposure and diminished physical functioning. However, studies that prospectively examine the relationship

between interpersonal abuse exposure and physical functioning across multiple years of observation are lacking. To address this literature gap, we prospectively evaluate the association between abuse exposure and physical functioning in a large, national cohort of post-menopausal women across 12 years of follow-up observation. METHODS: Multivariable logistic regression was used to measure the adjusted association between experiencing abuse and physical function score at baseline in 154,902 Women's Health Initiative (WHI) participants. Multilevel modeling, where the trajectories of decline in physical function were modeled as a function of time-varying abuse exposure, was used to evaluate the contribution of abuse to trajectories of physical function scores over time. RESULT: Abuse was prevalent among WHI participants, with 11 % of our study population reporting baseline exposure. Verbal abuse was the most commonly reported abuse type (10 %), followed by combined physical and verbal abuse (1 %), followed by physical abuse in the absence of verbal abuse (0.2 %). Abuse exposure (all types) was associated with diminished physical functioning, with women exposed to combined physical and verbal abuse presenting baseline physical functioning scores consistent with non-abused women 20 years senior. Results did not reveal a differential rate of decline over time in physical functioning based on abuse exposure. CONCLUSIONS: Taken together, our findings suggest a need for increased awareness of the prevalence of abuse exposure among postmenopausal women; they also underscore the importance of clinician's vigilance in their efforts toward the prevention, early detection and effective intervention with abuse exposure, including verbal abuse exposure, in post-menopausal women. Given our findings related to abuse exposure and women's diminished physical functioning at WHI baseline, our work illuminates a need for further study, particularly the investigation of this association in younger, pre-menopausal women so that the temporal ordering if this relationship may be better understood.

Carney, P. A., Frederick, P. D., Reisch, L. M., Knezevich, S., Piepkorn, M. W., Barnhill, R. L., et al. (2015). How concerns and experiences with medical malpractice affect dermatopathologists' perceptions of their diagnostic practices when interpreting cutaneous melanocytic lesions. *Journal of the American Academy of Dermatology,*
OBJECTIVE: We sought to identify characteristics associated with past malpractice lawsuits and how malpractice concerns may affect interpretive practices. METHODS: We surveyed 207 of 301

(68.8%) eligible dermatopathologists who interpret melanocytic skin lesions in 10 states. The survey assessed dermatopathologists' demographic and clinical practice characteristics, perceptions of how medical malpractice concerns could influence their interpretive practices, and past malpractice lawsuits. RESULTS: Of dermatopathologists, 33% reported past malpractice experiences. Factors associated with being sued included older age (57 vs 48 years, P 20 years: 52.9% vs 20.1%, P < .001). Of participants, 64% reported being moderately or extremely confident in their melanocytic interpretations. Although most dermatopathologists believed that malpractice concerns increased their likelihood of ordering specialized pathology tests, obtaining recuts, and seeking a second opinion, none of these practices were associated with past malpractice. Most dermatopathologists reported concerns about potential harms to patients that may result from their assessments of melanocytic lesions. LIMITATIONS: Limitations of this study include lack of validation of and details about the malpractice suits experienced by participating dermatopathologists. In addition, the study assessed perceptions of practice rather than actual practices that might be associated with malpractice incidents. CONCLUSIONS: Most dermatopathologists reported apprehension about how malpractice affects their clinical practice and are concerned about patient safety irrespective of whether they had actually experienced a medical malpractice suit.

Cassidy, P. B., Abdel-Malek, Z. A., & Leachman, S. A. (2015). Beyond red hair and sunburns: Uncovering the molecular mechanisms of MC1R signaling and repair of UV-induced DNA damage. *The Journal of Investigative Dermatology, 135*(12), 2918-2921.

Scientists at the University of Kentucky are unraveling the details of DNA-damage repair in the melanocyte, with an eye towards finding druggable targets for melanoma prevention. Jarret et al., (2015, this issue) report in this issue three new assays that can yield mechanistic information about nucleotide excision repair (NER) stimulated by cAMP-dependent signaling downstream of the melanocortin-1 receptor (MC1R).

Charlesworth, C. J., Peralta, C. A., & Odden, M. C. (2015). Functional status and antihypertensive therapy in older adults: A new perspective on old data. *American Journal of Hypertension,*

BACKGROUND: Functional status may be useful for identifying older adults who benefit from

lower blood pressure. We examined whether functional status modifies the effect of antihypertensive treatment among older adults. METHODS: Post hoc analyses of the Systolic Hypertension in the Elderly Program (SHEP), a randomized trial of antihypertensive therapy vs. placebo (1985-1991) in 4,736 adults aged 60 years or older with isolated systolic hypertension. Outcomes were all-cause death, cardiovascular (CV) death, myocardial infarction (MI), stroke, falls, and symptoms of hypotension. The effect modifier of interest was functional status, assessed by self-reported physical ability limitation (PAL). RESULTS: Among persons with no PAL, those receiving treatment had a lower rate of death, CV death, and MI compared with placebo (4.0, 2.9, and 4.2 per 1,000 person-years lower, respectively). In contrast, among persons with a PAL, those receiving treatment had a higher rate of death, CV death, and MI compared with placebo (8.6, 5.3, and 2.7 per 1,000 person-years higher, respectively). These patterns persisted in Cox models, although interaction terms did not reach statistical significance. Treatment remained protective for stroke regardless of functional status. The rate of falls associated with treatment differed by functional status; incidence-rate ratio = 0.81, 95% confidence interval (CI) = (0.66, 0.99), and 1.32, 95% CI = (0.87, 2.00) in participants without and with a PAL, respectively, in models adjusted for demographics and baseline blood pressure (P-value for interaction, 0.04). CONCLUSIONS: Functional status may modify the effect of antihypertensive treatment on MI, mortality, and falls, but not stroke, in older adults. Functional status should be examined in other trial settings.

Charry, J. D., Rubiano, A. M., Puyana, J. C., Carney, N., & David Adelson, P. (2015). Damage control of civilian penetrating brain injuries in environments of low neuro-monitoring resources. *British Journal of Neurosurgery,*

Introduction. Gunshot wounds to the head are more common in military settings. Recently, a damage control (DC) approach for the management of these lesions has been used in combat areas. The aim of this study was to evaluate the results of civilian patients with penetrating gunshot wounds to the head, managed with a strategy of early cranial decompression (ECD) as a DC procedure in a university hospital with few resources for intensive care unit (ICU) neuro-monitoring in Colombia. Materials and methods. Fifty-four patients were operated according to the DC strategy (<12 h after injury), over a 4-year period. Variables were analysed and results

were evaluated according to the Glasgow Outcome Scale (GOS) at 12 months post injury; a dichotomous variable was established as 'favourable' (GOS 4–5) or 'unfavourable' (GOS 1–3). A univariate analysis was performed using a χ2 test. Results. Forty (74.1%) of the patients survived and 36 (90%) of them had favourable GOS. Factors associated with adverse outcomes were: Injury Severity Score (ISS) greater than 25, bi-hemispheric involvement, intra-cerebral haematoma on the first CT, closed basal cisterns and non-reactive pupils in the emergency room. Conclusion. DC for neurotrauma with ECD is an option to improve survival and favourable neurological outcomes 12 months after injury in patients with penetrating traumatic brain injury treated in a university hospital with few resources for ICU neuro-monitoring. © 2015 Taylor & Francis

Chowdhury, R., Ashraf, H., Melanson, M., Tanada, Y., Nguyen, M., Silberbach, M., et al. (2015). Mouse model of human congenital heart disease: Progressive atrioventricular block induced by a heterozygous Nkx2-5 homeodomain missense mutation. *Circulation: Arrhythmia and Electrophysiology, 8*(5), 1255-1264.

Background - Heterozygous human NKX2-5 homeodomain (DNA-binding domain) missense mutations are highly penetrant for varied congenital heart defects, including progressive atrioventricular (AV) block requiring pacemaker implantation. We recently replicated this genetic defect in a murine knockin model, in which we demonstrated highly penetrant, pleiotropic cardiac anomalies. In this study, we examined postnatal AV conduction in the knockin mice. Methods and Results - A murine knockin model (Arg52Gly, Nkx2-5 +/R52G) in a 129/Sv background was analyzed by histopathology, surface, and telemetry ECG, and in vivo electrophysiology studies, comparing with control Nkx2-5 +/+ mice at diverse postnatal stages, ranging from postnatal day 1 (P1) to 17 months. PR prolongation (first degree AV block) was present at 4 weeks, 7 months, and 17 months of age, but not at P1 in the mutant mice. Advanced AV block was also occasionally demonstrated in the mutant mice. Electrophysiology studies showed that AV nodal function and right ventricular effective refractory period were impaired in the mutant mice, whereas sinus nodal function was not affected. AV nodal size was significantly smaller in the mutant mice than their controls at 4 weeks of age, corresponding to the presence of PR prolongation, but not P1, suggesting, at least in part, that the conduction abnormalities are the

result of a morphologically atrophic AV node. Conclusions - The highly penetrant and progressive AV block phenotype seen in human heterozygous missense mutations in NKX2-5 homeodomain was replicated in mice by knocking in a comparable missense mutation. © 2015 American Heart Association, Inc.

Coleman, K., Lutz, C. K., Worlein, J. M., Gottlieb, D. H., Peterson, E., Lee, G. H., et al. (2015). The correlation between alopecia and temperament in rhesus macaques (macaca mulatta) at four primate facilities. *American Journal of Primatology,*

Alopecia is a ubiquitous, multifaceted problem at facilities caring for captive rhesus macaques. There is a wide range of potential etiologies for the hair loss, including compromised immune function, dermatological pathologies, and environmental factors. However, few studies have examined whether various temperamental traits affect vulnerability to develop alopecia. We examined the correlation between alopecia and temperament in 101 (51M) indoor-housed rhesus macaques at four national primate centers. We utilized a cage side version of the Human Intruder test (HIT) to assess response to four conditions: no human present (Alone), human intruder standing next to the cage without making eye contact (Profile), intruder making direct eye contact (Stare) and intruder with back turned (Back). Behavior from all videos was quantified at one facility. We used generalized linear modeling to examine the relationship between behavior on the HIT and alopecia, controlling for facility, age, and sex. There was a significant negative correlation between alopecia and various behaviors associated with an inhibited or anxious temperament, including self-directed behavior (beta = -0.15, P < 0.001) and freeze in the Profile period (beta = -0.0092, P < 0.001), and defensive behaviors (beta = -0.0094, P < 0.001) and time spent in the back of the cage in the Stare period (beta = -0.0023, P = 0.015). Individuals with an inhibited or anxious temperament had less alopecia than others. Further, there were facility differences with respect to several variables on the HIT, including defensive behavior in Stare and freeze in Profile. These results suggest that temperament can influence the development of alopecia in rhesus macaques. Our results also highlight the degree to which facility differences can affect outcomes on standardized behavioral tests. Am. J. Primatol. (c) 2015 Wiley Periodicals, Inc.

Conrad, E., Dai, C., Spaeth, J., Guo, M., Cyphert, H. A., Scoville, D., et al. (2015). The MAFB transcription factor impacts islet alpha-cell function in rodents and represents a unique signature of primate islet beta-cells. *American Journal of Physiology.Endocrinology and Metabolism, ,* ajpendo.00285.2015.

Analysis of MafB-/- mice suggested that this transcription factor was essential to islet alpha- and beta-cell formation during development, although the postnatal physiological impact could not be studied because these mutants died due to problems in neural development. Pancreas-wide mutant mice were generated to compare the postnatal significance of MafB (MafBDeltapanc) and MafA/B (MafABDeltapanc) to deficiencies associated with the related, beta-cell-enriched MafA mutant (MafADeltapanc). Insulin+ cell production and beta-cell activity was merely delayed in MafBDeltapanc islets until MafA was comprehensively expressed in this cell population. We propose that MafA compensates for the absence of MafB in MafBDeltapanc mice, which is supported by the death of MafABDeltapanc mice soon after birth from hyperglycemia. However, glucose-induced glucagon secretion was compromised in adult MafBDeltapanc islet alpha-cells. Based upon these results, we conclude that MafB is only essential to islet alpha-cell activity, and not beta-cell. Interestingly, a notable difference between mice and humans is that MAFB is coexpressed with MAFA in adult human islet beta-cells. Here we show that non-human primate (NHP) islet alpha- and beta-cells also produce MAFB, implying that MAFB represents a unique signature and likely important regulator of the primate islet beta-cell.

Costantino, C., Thomas, G. V., Ryan, C., Coakley, F. V., & Troxell, M. L. (2015). Metastatic renal cell carcinoma without evidence of a renal primary. *International Urology and Nephrology,*

PURPOSE: Metastatic renal cell carcinoma (RCC), without an identified kidney primary, has been reported rarely. We report a patient with RCC metastatic to bilateral adrenal glands and liver, without an apparent renal primary. We detail the immunohistochemical and molecular studies employed to substantiate the diagnosis of RCC and direct therapy. METHODS: Histopathologic findings were correlated with imaging data and supplemented by a panel of immunohistochemical stains, as well as tumor sequence analysis. RESULTS: Despite the presence of bilateral adrenal masses and lack of tumor within kidney parenchyma, the diagnosis of RCC was substantiated by immunohistochemistry (RCC+/PAX2+/PAX8+/Melan-A-/SF-1- among others) and molecular

genetic analysis, harboring mutations in VHL, TP53, KDM5C, and PBRM1. After debulking surgery, based on the diagnosis of RCC and the molecular profile, the patient was treated with a tyrosine kinase inhibitor (sunitinib), resulting in stablilization of disease. CONCLUSIONS: This case illustrates the role of mutational analysis in carcinomas with rare or unusual presentations, such as metastatic RCC without a renal primary.

Crusoe, M. R., Alameldin, H. F., Awad, S., Boucher, E., Caldwell, A., Cartwright, R., et al. (2015). The khmer software package: Enabling efficient nucleotide sequence analysis. *F1000research, 4*, 900. The khmer package is a freely available software library for working efficiently with fixed length DNA words, or k-mers. khmer provides implementations of a probabilistic k-mer counting data structure, a compressible De Bruijn graph representation, De Bruijn graph partitioning, and digital normalization. khmer is implemented in C++ and Python, and is freely available under the BSD license at https://github.com/dib-lab/khmer/.

Dagan, M. P., & Hall, S. B. (2015). The equilibrium spreading tension of pulmonary surfactant. *Langmuir : The ACS Journal of Surfaces and Colloids,* Monomolecular films at an air/water interface coexist at the equilibrium spreading tension (gammae) with the bulk phase from which they form. For individual phospholipids, gammae is single-valued, and separates conditions at which hydrated vesicles adsorb from tensions at which overcompressed monolayers collapse. With pulmonary surfactant, isotherms show that monolayers compressed on the surface of bubbles coexist with the three-dimensional collapsed phase over a range of surface tensions. gammae therefore represents a range rather than a single value of surface tension. Between the upper and lower ends of this range, rates of collapse for spread and adsorbed films decrease substantially. Changes during adsorption across this narrow region of coexistence between the two- and three-dimensional structures at least partially explain how alveolar films of pulmonary surfactant become resistant to collapse.

Davis, M. M., Spurlock, M., Dulacki, K., Meath, T., Li, H. G., McCarty, D., et al. (2015). Disparities in alcohol, drug use, and mental health condition prevalence and access to care in rural, isolated, and reservation areas: Findings from the south dakota health survey. *The Journal of Rural Health : Official Journal of the American Rural Health Association and the National Rural Health Care*

Association,

PURPOSE: Research on urban/rural disparities in alcohol, drug use, and mental health (ADM) conditions is inconsistent. This study describes ADM condition prevalence and access to care across diverse geographies in a predominantly rural state. METHODS: Multimodal cross-sectional survey in South Dakota from November 2013 to October 2014, with oversampling in rural areas and American Indian reservations. Measures assessed demographic characteristics, ADM condition prevalence using clinical screenings and participant self-report, perceived need for treatment, health service usage, and barriers to obtaining care. We tested for differences among urban, rural, isolated, and reservation geographic areas, controlling for participant age and gender. FINDINGS: We analyzed 7,675 surveys (48% response rate). Generally, ADM condition prevalence rates were not significantly different across geographies. However, respondents in isolated and reservation areas were significantly less likely to have access to primary care. Knowledge of treatment options was significantly lower in isolated regions and individuals in reservation areas had significantly lower odds of reporting receipt of all needed care. Across the sample there was substantial discordance between ADM clinical screenings and participant self-reported need; 98.1% of respondents who screened positive for alcohol or drug misuse and 63.8% of respondents who screened positive for a mental health condition did not perceive a need for care. CONCLUSION: In a predominantly rural state, geographic disparities in ADM conditions are related to differences in access as opposed to prevalence, particularly for individuals in isolated and reservation areas. Educational interventions about ADM condition characteristics may be as important as improving access to care.

De Boer, E. (2015). Physics underlying the physiology of the ear. *Journal of the Acoustical Society of America, 138*(4), 2554-2560.

Deem, S., Yanez, D., Sissons-Ross, L., Elrod-Broeckel, J. A., Daniel, S., & Treggiari, M. (2015). Randomized pilot trial of endotracheal tubes to prevent ventilator-associated pneumonia. *Annals of the American Thoracic Society,*

INTRODUCTION: Ventilator-associated pneumonia (VAP) is a prevalent and expensive nosocomial infection related to instrumentation of the airway with an endotracheal tube (ETT), enabling

microaspiration of contaminated secretions. Modification of the ETT design to reduce microaspiration and/or biofilm formation may play an important role in VAP prevention. However, there is insufficient evidence to provide strong recommendations regarding the use of modified ETT and unaddressed safety concerns. We performed a pilot, randomized controlled trial comparing two modified ETTs designed specifically to prevent VAP, with the standard ETT to test the feasibility of and inform planning for a large, pivotal randomized trial. METHODS: This study was conducted with IRB approval under exception from informed consent. We randomized in a blinded fashion patients undergoing emergency endotracheal intubation both out-of- and in-hospital to receive one of three different ETT types: 1) Polyurethane-cuffed tube (PUC-ETT); 2) Polyurethane-cuffed tube equipped with a port for continuous aspiration of subglottic secretions (PUC-CASS-ETT), and 3) Standard, polyvinylchloride-cuffed tube (PVC-ETT). In addition to investigating feasibility and safety, the study co-primary endpoints were tracheal bacterial colonization reaching a CFU count >106 CFUs/mL and the incidence of invasively-diagnosed VAP. MEASUREMENTS AND MAIN RESULTS: A total of 102 subjects were randomized and met eligibility criteria. Randomization procedures performed well and integrity of blinding at randomization was maintained. The majority of intubations occurred in the hospital setting (n = 77) and the remainder occurred out-of-hospital (n = 25). Compared with the PVC-ETT, there were no significant differences in tracheal colonization for PUC-ETT (OR: 0.98; 95%CI: 0.31, 3.09) or for PUC-CASS-ETT (OR: 1.26; 95%CI: 0.42-3.76). There were no differences in the risk of invasively-diagnosed VAP (OR: 1.14; 95%CI: 0.21, 6.08 for PUC-ETT, and OR: 1.47; 95%CI: 0.30, 7.10 for PUC-CASS-ETT), or clinically-diagnosed VAP by either clinical signs or chest radiograph criteria. We did not observe unexpected or serious adverse events related to the devices. CONCLUSIONS: A randomized trial of ETTs inserted during emergency intubation for the prevention of VAP is feasible and did not appear to carry heightened safety concerns. These preliminary data did not suggest different patterns of tracheal colonization or occurrence of VAP between the study groups. Clinical Trial registered with ClinicalTrials.gov (NCT01744483).

DeLoughery, T. G. (2015). Preface. *Hemostasis and Thrombosis, Third Edition,* , v-vi.

Devlin, N., Herdman, M., Pavesi, M., Phung, D., Naidoo, S., Beer, T. M., et al. (2015). Health-related quality of life (hrqol) benefits of enzalutamide in patients with metastatic castration-resistant prostate cancer (mcrpc): An in-depth analysis of eq-5d data from the prevail trial. *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 18*(7), A475.

Dijkstra, B. W., Horak, F. B., Kamsma, Y. P., & Peterson, D. S. (2015). Older adults can improve compensatory stepping with repeated postural perturbations. *Frontiers in Aging Neuroscience, 7*, 201.

The ability to respond quickly and accurately to an external perturbation with a stepping response is critical to avoid falls and this ability is impaired in older, compared to young adults. However, little is known about whether young and older adults improve compensatory stepping responses similarly with practice. This study compares the extent to which young and older adults can improve, retain, and generalize postural compensatory steps in response to external perturbations. Centre of mass displacement, step characteristics and lower leg muscle activation latencies were measured during one training session of compensatory stepping in response to large surface translations in 13 young and 12 older adults. Retention was tested 24 h later. Older adults decreased their center of mass displacements over repeated exposure to large surface translations in both the anterior and posterior directions and retained these improvements. In contrast, young adults only showed adaptation and retention of forward stepping responses. Neither group was able to generalize improvements in stepping responses across directions. These results suggest step training may be beneficial for older adults, however additional, multidirectional training may be necessary to facilitate generalization of postural stepping responses for any direction of a slip or trip.

Dong, J., Tang, M., Zhang, Y., Jia, Y., Zhang, H., Jia, Z., et al. (2015). Comparison of anterior segment biometric measurements between pentacam HR and IOLMaster in normal and high myopic eyes. *PloS One, 10*(11), e0143110.

PURPOSE: To compare the anterior chamber depth (ACD), keratometry (K) and astigmatism measurements taken by IOLMaster and Pentacam HR in normal and high myopic (HM) eyes.

DESIGN: A prospective observational case series. METHODS: Sixty-six normal eyes and 59 HM eyes underwent ACD, keratometry and astigmatism measurements with both devices. Axial length (AL) was measured on IOLMaster. The interdevice agreement was evaluated using the Bland-Altman analysis and paired t-test. The correlations between age and AL & ACD were analyzed. Vector analysis was used to compare astigmatism measurements. RESULTS: The ACD from IOLMaster and Pentacam HR was different for the normal group (P = 0.003) but not for the HM group (P = 0.280). IOLMaster demonstrated higher steep K and mean K values than Pentacam HR for both normal and HM groups (P<0.001 for all). IOLMaster also have higher flat K values for the HM groups (P<0.001) but were statistically equivalent with Pentacam HR for the normal group (P = 0.119) IOLMaster and Pentacam HR were different in astigmatism measurements for the normal group but were statistically equivalent for the HM group. For the normal group, age was negatively correlated with AL, IOLMaster ACD and Pentacam HR ACD (r = -0.395, P = 0.001; r = -0.715, P < 0.001; r = -0.643, P < 0.001). For the HM group, age was positively correlated with AL but negatively correlated with IOLMaster ACD and Pentacam HR ACD (r = 0.377, P = 0.003; r = -0.392, P = 0.002; r = -0.616, P < 0.001). CONCLUSIONS: The IOLMaster and Pentacam HR have significant difference in corneal power measurements for both normal and HM groups. The two instruments also differ in ACD and astigmatism measurement for the normal group. Therefore, a single instrument is recommended for studying longitudinal changes in anterior segment biometric measurements. Age should be considered as an influencing factor for both AL and ACD values in the normal and HM group.

Donley, N., Jaruga, P., Coskun, E., Dizdaroglu, M., McCullough, A. K., & Lloyd, R. S. (2015). Small molecule inhibitors of 8-oxoguanine DNA glycosylase-1 (OGG1). *ACS Chemical Biology, 10*(10), 2334-2343.

The DNA base excision repair (BER) pathway, which utilizes DNA glycosylases to initiate repair of specific DNA lesions, is the major pathway for the repair of DNA damage induced by oxidation, alkylation, and deamination. Early results from clinical trials suggest that inhibiting certain enzymes in the BER pathway can be a useful anticancer strategy when combined with certain DNA-damaging agents or tumor-specific genetic deficiencies. Despite this general validation of BER enzymes as drug targets, there are many enzymes that function in the BER pathway that

have few, if any, specific inhibitors. There is a growing body of evidence that suggests inhibition of 8-oxoguanine DNA glycosylase-1 (OGG1) could be useful as a monotherapy or in combination therapy to treat certain types of cancer. To identify inhibitors of OGG1, a fluorescence-based screen was developed to analyze OGG1 activity in a high-throughput manner. From a primary screen of ~50 000 molecules, 13 inhibitors were identified, 12 of which were hydrazides or acyl hydrazones. Five inhibitors with an IC50 value of less than 1 μM were chosen for further experimentation and verified using two additional biochemical assays. None of the five OGG1 inhibitors reduced DNA binding of OGG1 to a 7,8-dihydro-8-oxoguanine (8-oxo-Gua)-containing substrate, but all five inhibited Schiff base formation during OGG1-mediated catalysis. All of these inhibitors displayed a >100-fold selectivity for OGG1 relative to several other DNA glycosylases involved in repair of oxidatively damaged bases. These inhibitors represent the most potent and selective OGG1 inhibitors identified to date. © 2015 American Chemical Society.

Dotson, A. L., Wang, J., Chen, Y., Manning, D., Nguyen, H., Saugstad, J. A., et al. (2015). Sex differences and the role of PPAR alpha in experimental stroke. *Metabolic Brain Disease,* Males and females respond differently to stroke. Moreover, females often experience worse long-term stroke outcomes. Fenofibrate, a peroxisome proliferator-activated receptor alpha (PPARalpha) agonist has been shown to improve stroke outcome and resolve neuroinflammation in male mice. The present study compares the effect of pretreatment with fenofibrate versus vehicle control in male and female mice during experimental stroke. Mice were treated with low-dose fenofibrate 30 min before and once a day for three additional days after stroke onset. We observed a reduction in infarct volume in male mice 96 h post-stroke with low-dose fenofibrate pretreatment that was due to increase of an M2 macrophage phenotype in the brain and an increase in regulatory cells in the periphery. These outcomes were not replicated in females, likely due to the lower PPARalpha expression in cells and tissues in females vs males. We conclude that PPARalpha agonist treatment prior to stroke is neuroprotective in males but not females. These findings indicate PPARalpha as a probable mechanism of sex difference in stroke outcome and support the need for representation of females in stroke therapy research.

Doyle, J. J., Doyle, A. J., Wilson, N. K., Habashi, J. P., Bedja, D., Whitworth, R. E., et al. (2015). A deleterious gene-by-environment interaction imposed by calcium channel blockers in marfan syndrome. *Elife, 4*(OCTOBER2015)

Calcium channel blockers (CCBs) are prescribed to patients with Marfan syndrome for prophylaxis against aortic aneurysm progression, despite limited evidence for their efficacy and safety in the disorder. Unexpectedly, Marfan mice treated with CCBs show accelerated aneurysm expansion, rupture, and premature lethality. This effect is both extracellular signal-regulated kinase (ERK1/2) dependent and angiotensin-II type 1 receptor (AT1R) dependent. We have identified protein kinase C beta (PKCβ) as a critical mediator of this pathway and demonstrate that the PKCβ inhibitor enzastaurin, and the clinically available anti-hypertensive agent hydralazine, both normalize aortic growth in Marfan mice, in association with reduced PKCβ and ERK1/2 activation. Furthermore, patients with Marfan syndrome and other forms of inherited thoracic aortic aneurysm taking CCBs display increased risk of aortic dissection and need for aortic surgery, compared to patients on other antihypertensive agents. © 2015, eLife Sciences Publications Ltd. All Rights Reserved.

DuBois, B. N., Pearson, J., Mahmood, T., Thornburg, K., & Cherala, G. (2015). Furosemide pharmacokinetics in adult rats become abnormal with an adverse intrauterine environment and modulated by a post-weaning high-fat diet. *Basic & Clinical Pharmacology & Toxicology,*

Adult individuals born with intrauterine growth restriction (IUGR) have physiological maladaptations that significantly increase risk of chronic disease. We hypothesized that such abnormalities in organ function would alter pharmacokinetics throughout life, exacerbated by environmental mismatch. Pregnant and lactating rats were fed either a purified control diet (18% protein) or low protein diet (9% protein) to produce IUGR offspring. Offspring were weaned onto either laboratory chow (11% fat) or high-fat diet (45% fat). Adult offspring (5 months old) were dosed with furosemide (10 mg/kg i.p.) and serum and urine collected. The overall exposure profile in IUGR males was significantly reduced due to a ~35% increase in both clearance and volume of distribution. Females appeared resistant to the IUGR phenotype. The effects of the high-fat diet trended in the opposite direction to that of IUGR, with increased drug exposure due to decreases in both clearance (31% males, 46% females) and volume of distribution (24%

males, 44% females), with a 10% longer half-life in both genders. The alterations in furosemide pharmacokinetics and pharmacodynamics were explained by changes in the expression of renal organic anion transporters-1 and -3, and sodium-potassium-chloride cotransporter-2. In summary, this study suggests that IUGR and diet interact to produce sub-populations with similar body weights but dissimilar pharmacokinetic profiles; this underlines the limitation of one-size-fits-all dosing which does not account for physiological differences in body composition resulting from IUGR and diet.

Ellison, D. H. (2015). Outstanding translational science at american society of hypertension 2015. *Journal of the American Society of Hypertension : JASH, 9*(11), 828-830.

Erdman, J. W.,Jr, Smith, J. W., Kuchan, M. J., Mohn, E. S., Johnson, E. J., Rubakhin, S. S., et al. (2015). Lutein and brain function. *Foods (Basel, Switzerland), 4*(4), 547-564.
Lutein is one of the most prevalent carotenoids in nature and in the human diet. Together with zeaxanthin, it is highly concentrated as macular pigment in the foveal retina of primates, attenuating blue light exposure, providing protection from photo-oxidation and enhancing visual performance. Recently, interest in lutein has expanded beyond the retina to its possible contributions to brain development and function. Only primates accumulate lutein within the brain, but little is known about its distribution or physiological role. Our team has begun to utilize the rhesus macaque (Macaca mulatta) model to study the uptake and bio-localization of lutein in the brain. Our overall goal has been to assess the association of lutein localization with brain function. In this review, we will first cover the evolution of the non-human primate model for lutein and brain studies, discuss prior association studies of lutein with retina and brain function, and review approaches that can be used to localize brain lutein. We also describe our approach to the biosynthesis of 13C-lutein, which will allow investigation of lutein flux, localization, metabolism and pharmacokinetics. Lastly, we describe potential future research opportunities.

Farrell, D. H. (2015). Lucky 13. *Blood, 126*(20), 2261-2262.

Ferzoco, S., Clara, E. S., Tang, S. W., Hu, J., Tan, W. B., Shabbir, A., et al. (2015). Mesh & prosthesis. *Hernia : The Journal of Hernias and Abdominal Wall Surgery, 19 Suppl 1*, S147-56.

Fink, H. A., Litwack-Harrison, S., Taylor, B. C., Bauer, D. C., Orwoll, E. S., Lee, C. G., et al. (2015).

Clinical utility of routine laboratory testing to identify possible secondary causes in older men with

osteoporosis: The osteoporotic fractures in men (MrOS) study. *Osteoporosis International,*

Summary: We investigated the value of routine laboratory testing for identifying underlying

causes in older men diagnosed with osteoporosis. Most osteoporotic and nonosteoporotic men

had ≥1 laboratory abnormality. Few individual laboratory abnormalities were more common in

osteoporotic men. The benefit of routine laboratory testing in older osteoporotic men may be low.

Introduction: To evaluate the utility of recommended laboratory testing to identify secondary

causes in older men with osteoporosis, we examined prevalence of laboratory abnormalities in

older men with and without osteoporosis. Methods: One thousand five hundred seventy-two men

aged ≥65 years in the Osteoporotic Fractures in Men study completed bone mineral density

(BMD) testing and a battery of laboratory measures, including serum calcium, phosphorus,

alkaline phosphatase, parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), 25-OH

vitamin D, total testosterone, spot urine calcium/creatinine ratio, spot urine albumin/creatinine

ratio, creatinine-derived estimated glomerular filtration rate, 24-h urine calcium, and 24-h urine

free cortisol. Using cross-sectional analyses, we calculated prevalence ratios (PRs) and 95 %

confidence intervals (CI) for the association of any and specific laboratory abnormalities with

osteoporosis and the number of men with osteoporosis needed to test to identify one additional

laboratory abnormality compared to testing men without osteoporosis. Results: Approximately 60

% of men had ≥1 laboratory abnormality in both men with and without osteoporosis. Among

individual tests, only vitamin D insufficiency (PR, 1.13; 95 % CI, 1.05–1.22) and high alkaline

phosphatase (PR, 3.05; 95 % CI, 1.52–6.11) were more likely in men with osteoporosis.

Hypercortisolism and hyperthyroidism were uncommon and not significantly more frequent in

men with osteoporosis. No osteoporotic men had hypercalciuria. Conclusions: Though most of

these older men had ≥1 laboratory abnormality, few routinely recommended individual tests

were more common in men with osteoporosis than in those without osteoporosis. Possibly

excepting vitamin D and alkaline phosphatase, benefit of routine laboratory testing to identify

possible secondary causes in older osteoporotic men appears low. Results may not be

generalizable to younger men or to older men in whom history and exam findings raise clinical

suspicion for a secondary cause of osteoporosis. © 2015 International Osteoporosis Foundation and National Osteoporosis Foundation

Finnerty, N. M., Rodriguez, R. M., Carpenter, C. R., Sun, B. C., Theyyunni, N., Ohle, R., et al. (2015). Clinical decision rules for diagnostic imaging in the emergency department: A research agenda. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine,* BACKGROUND: Major gaps persist in the development, validation, and implementation of clinical decision rules (CDRs) for diagnostic imaging. OBJECTIVES: The objective of this working group and article was to generate a consensus-based research agenda for the development and implementation of CDRs for diagnostic imaging in the emergency department (ED). METHODS: The authors followed consensus methodology, as outlined by the journal Academic Emergency Medicine (AEM), combining literature review, electronic surveys, telephonic communications, and a modified nominal group technique. Final discussions occurred in person at the 2015 AEM consensus conference. RESULTS: A research agenda was developed, prioritizing the following questions: 1) what are the optimal methods to justify the derivation and validation of diagnostic imaging CDRs, 2) what level of evidence is required before disseminating CDRs for widespread implementation, 3) what defines a successful CDR, 4) how should investigators best compare CDRs to clinical judgment, and 5) what disease states are amenable (and highest priority) to development of CDRs for diagnostic imaging in the ED? CONCLUSIONS: The concepts discussed herein demonstrate the need for further research on CDR development and implementation regarding diagnostic imaging in the ED. Addressing this research agenda should have direct applicability to patients, clinicians, and health care systems.

Fischer, S., Lin, D., Simon, R. M., Howard, L. E., Aronson, W. J., Terris, M. K., et al. (2015). Do all men with pathological gleason score 8-10 prostate cancer have poor outcomes? results from the SEARCH database. *BJU International,*
Objective: To determine whether there are subsets of men with pathological high grade prostate cancer (Gleason score 8-10) with particularly high or low 2-year biochemical recurrence (BCR) risk after radical prostatectomy (RP) when stratified into groups based on combinations of pathological features, such as surgical margin status, extracapsular extension (ECE) and seminal

vesicle invasion (SVI). Materials and Methods: We identified 459 men treated with RP with pathological Gleason score 8-10 prostate cancer in the SEARCH database. The men were stratified into five groups based on pathological characteristics: group 1, men with negative surgical margins (NSMs) and no ECE; group 2, men with positive surgical margin (PSMs) and no ECE; group 3, men with NSMs and ECE; group 4, men with PSMs and ECE; and group 5, men with SVI. Cox proportional hazards models and the log-rank test were used to compare BCR among the groups. Results: At 2 years after RP, pathological group was significantly correlated with BCR (log-rank, $P < 0.001$) with patients in group 5 (+SVI) having the highest BCR risk (66%) and those in group 1 (NSMs and no ECE) having the lowest risk (14%). When we compared groups 2, 3, and 4, with each other, there was no significant difference in BCR among the groups (~50% 2-year BCR risk; log-rank $P = 0.28$). Results were similar when adjusting for prostate-specific antigen, age, pathological Gleason sum and clinical stage, or after excluding men who received adjuvant therapy. Conclusions: In patients with high grade (Gleason score 8-10) prostate cancer after RP, the presence of either PSMs, ECE or SVI was associated with an increased risk of early BCR, with a 2-year BCR risk of ≥50%. Conversely, men with organ-confined margin-negative disease had a very low risk of early BCR despite Gleason score 8-10 disease. © 2015 BJU International.

Flanigan, M., Heilman, J. A., Johnson, T., & Yarris, L. M. (2015). Teaching and assessing ED handoffs: A qualitative study exploring resident, attending, and nurse perceptions. *Western Journal of Emergency Medicine, 16*(6), 823-829.

Introduction: The Accreditation Council for Graduate Medical Education requires that residency programs ensure resident competency in performing safe, effective handoffs. Understanding resident, attending, and nurse perceptions of the key elements of a safe and effective emergency department (ED) handoff is a crucial step to developing feasible, acceptable educational interventions to teach and assess this fundamental competency. The aim of our study was to identify the essential themes of ED-based handoffs and to explore the key cultural and interprofessional themes that may be barriers to developing and implementing successful ED-based educational handoff interventions. Methods: Using a grounded theory approach and constructivist/interpretivist research paradigm, we analyzed data from three primary and one

confirmatory focus groups (FGs) at an urban, academic ED. FG protocols were developed using open-ended questions that sought to understand what participants felt were the crucial elements of ED handoffs. ED residents, attendings, a physician assistant, and nurses participated in the FGs. FGs were observed, hand-transcribed, audiorecorded and subsequently transcribed. We analyzed data using an iterative process of theme and subtheme identification. Saturation was reached during the third FG, and the fourth confirmatory group reinforced the identified themes. Two team members analyzed the transcripts separately and identified the same major themes. Results: ED providers identified that crucial elements of ED handoff include the following: 1) Culture (provider buy-in, openness to change, shared expectations of sign-out goals); 2) Time (brevity, interruptions, waiting); 3) Environment (physical location, ED factors); 4) Process (standardization, information order, tools). Conclusion: Key participants in the ED handoff process perceive that the crucial elements of intershift handoffs involve the themes of culture, time, environment, and process. Attention to these themes may improve the feasibility and acceptance of educational interventions that aim to teach and assess handoff competency. © 2015 by the article author(s).

Fleseriu, M., Pivonello, R., Young, J., Hamrahian, A. H., Molitch, M. E., Shimizu, C., et al. (2015). Osilodrostat, a potent oral 11beta-hydroxylase inhibitor: 22-week, prospective, phase II study in cushing's disease. *Pituitary,*

PURPOSE: In a 10-week proof-of-concept study (LINC 1), the potent oral 11beta-hydroxylase inhibitor osilodrostat (LCI699) normalized urinary free cortisol (UFC) in 11/12 patients with Cushing's disease. The current 22-week study (LINC 2; NCT01331239) further evaluated osilodrostat in patients with Cushing's disease. METHODS: Phase II, open-label, prospective study of two patient cohorts. Follow-up cohort: 4/12 patients previously enrolled in LINC 1, offered re-enrollment if baseline mean UFC was above ULN. Expansion cohort: 15 newly enrolled patients with baseline UFC > 1.5 x ULN. In the follow-up cohort, patients initiated osilodrostat twice daily at the penultimate efficacious/tolerable dose in LINC 1; dose was adjusted as needed. In the expansion cohort, osilodrostat was initiated at 4 mg/day (10 mg/day if baseline UFC > 3 x ULN), with dose escalated every 2 weeks to 10, 20, 40, and 60 mg/day until UFC /=50 % decrease from baseline) at weeks 10 and 22. RESULTS: Overall response rate was 89.5 % (n/N =

17/19) at 10 weeks and 78.9 % (n/N = 15/19) at 22 weeks; at week 22, all responding patients had UFC </= ULN. The most common AEs observed during osilodrostat treatment were nausea, diarrhea, asthenia, and adrenal insufficiency (n = 6 for each). New or worsening hirsutism (n = 2) and/or acne (n = 3) were reported among four female patients, all of whom had increased testosterone levels. CONCLUSIONS: Osilodrostat treatment reduced UFC in all patients; 78.9 % (n/N = 15/19) had normal UFC at week 22. Treatment with osilodrostat was generally well tolerated.

Folk, J. C., Adelman, R. A., Flaxel, C. J., Hyman, L., Pulido, J. S., & Olsen, T. W. (2015). Idiopathic epiretinal membrane and vitreomacular traction preferred practice pattern guidelines. *Ophthalmology,*

Folmer, R. L., & Theodoroff, S. M. (2015). Assessment of blinding in a tinnitus treatment trial-reply. *JAMA Otolaryngology-- Head & Neck Surgery, 141*(11), 1031-1032.

Forbes, S. C., Willcocks, R. J., Rooney, W. D., Walter, G. A., & Vandenborne, K. (2015). MRI quantifies neuromuscular disease progression. *The Lancet.Neurology,*

Forciea, M. A., Humphrey, L. L., & Qaseem, A. (2015). In response. *Annals of Internal Medicine, 163*(8), 646.

Forciea, M. A., Humphrey, L. L., & Qaseem, A. (2015). In response. *Annals of Internal Medicine, 163*(8), 649.

Friend, R., & Bennett, R. M. (2015). Evaluating disease severity in chronic pain patients with and without fibromyalgia: A comparison of the symptom impact questionnaire and the polysymptomatic distress scale. *The Journal of Rheumatology, 42*(12), 2404-2411. OBJECTIVE: To compare the relative effectiveness of the Polysymptomatic Distress Scale (PSD) with the Symptom Impact Questionnaire (SIQR), the disease-neutral revision of the updated Fibromyalgia Impact Questionnaire (FIQR), in their ability to assess disease activity in patients with rheumatic disorders both with and without fibromyalgia (FM). METHODS: The study included 321 patients from 8 clinical practices with some 16 different chronic pain disorders. Disease

severity was assessed by the Medical Outcomes Study Short Form-36 (SF-36). Univariate analyses were used to assess the magnitude of PSD and SIQR correlations with SF-36 subscales. Hierarchical stepwise regression was used to evaluate the unique contribution of the PSD and SIQR to the SF-36. Random forest regression probed the relative importance of the SIQR and PSD components as predictors of SF-36. RESULTS: The correlations with the SF-36 subscales were significantly higher for the SIQR (0.48 to 0.78) than the PSD (0.29 to 0.56; $p < 0.001$). Stepwise regression revealed that the SIQR was contributing additional unique variance on SF-36 subscales, which was not the case for the PSD. Random forest regression showed SIQR Function, Symptoms, and Global Impact subscales were more important predictors of SF-36 than the PSD. The single SIQR pain item contributed 55% of SF-36 pain variance compared to 23% with the 19-point WPI (the Widespread Pain Index component of PSD). CONCLUSION: The SIQR, the disease-neutral revision of the updated FIQ, has several important advantages over the PSD in the evaluation of disease severity in chronic pain disorders.

Frishman, G. N., Bell, C. L., Botros, S., Brost, B. C., Robinson, R. D., Steinauer, J., et al. (2015). Applying to subspecialty fellowship: Clarifying the confusion and conflicts! *American Journal of Obstetrics and Gynecology,*

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

of residents needing time off for interviews during any one time period. In addition, a series of formal discussions should take place between subspecialties related to these issues as well as within subspecialties to facilitate coordination.

Garbati, M. R., Welgan, C. A., Landefeld, S. H., Newell, L. F., Agarwal, A., Dunlap, J. B., et al. (2015). Mutant calreticulin-expressing cells induce monocyte hyperreactivity through a paracrine mechanism. *American Journal of Hematology,*
Mutations in the calreticulin gene (CALR) were recently identified in approximately 70-80% of patients with JAK2-V617F-negative essential thrombocytosis and primary myelofibrosis. All frameshift mutations generate a recurring novel C-terminus. Here we provide evidence that mutant calreticulin does not accumulate efficiently in cells and is abnormally enriched in the nucleus and extracellular space compared to wildtype calreticulin. The main determinant of these findings is the loss of the calcium-binding and KDEL domains. Expression of type I mutant CALR in Ba/F3 cells confers minimal IL-3-independent growth. Interestingly, expression of type I and type II mutant CALR in a non-hematopoietic cell line does not directly activate JAK/STAT signaling compared to JAK2-V617F expression. These results led us to investigate paracrine mechanisms of JAK/STAT activation. Here we show that conditioned media from cells expressing type I mutant CALR exaggerate cytokine production from normal monocytes with or without treatment with a toll-like receptor agonist. These effects are not dependent on the novel C-terminus. These studies offer novel insights into the mechanism of JAK/STAT activation in patients with JAK2-V617F-negative essential thrombocytosis and primary myelofibrosis. This article is protected by copyright. All rights reserved.

Gaskin, D., Kroll, N. A., Ochs, A. A., Schreiber, M. A., & Pandalai, P. K. (2015). Far forward anesthesia and massive blood transfusion: Two cases revealing the challenge of damage control resuscitation in an austere environment. *AANA Journal, 83*(5), 337-343.
Since the beginning of Operation Enduring Freedom and Operation Iraqi Freedom, the US military has treated more than 51,000 casualties and sustained more than 6,600 deaths. The past decade of conflict has solidified major advances in the use of blood component therapy and the liberal use of fresh whole blood during damage control resuscitation. This resuscitation strategy,

combined with far forward damage control surgery, rapid aeromedical evacuation, and major improvements in critical care air transportation and personal protective equipment has led to a 90% to 92% survival rate in US casualties. We describe 2 cases treated by a Forward Surgical Team serving in Afghanistan during Operation Enduring Freedom in 2014. Both patients suffered severe trauma and required massive blood transfusion and damage control surgery. In describing these 2 cases, we wish to share our experience with damage control resuscitation in an austere environment, as well as advocate for the critical role of the Certified Registered Nurse Anesthetist in advancing the knowledge and execution of this lifesaving strategy in both military and civilian trauma centers. In addition, we suggest alternatives to the current transfusion strategy, which will mitigate limitations currently encountered.

Gelbard, A., Donovan, D. T., Ongkasuwan, J., Nouraei, S. A., Sandhu, G., Benninger, M. S., et al. (2015). Disease homogeneity and treatment heterogeneity in idiopathic subglottic stenosis. *The Laryngoscope,*
OBJECTIVES/HYPOTHESIS: Idiopathic subglottic stenosis (iSGS) is a rare and potentially life-threatening disease marked by recurrent and progressive airway obstruction frequently requiring repeated surgery to stabilize the airway. Unknown etiology and low disease prevalence have limited the ability to characterize the natural history of iSGS and resulted in variability in surgical management. It is uncertain how this variation relates to clinical outcomes. STUDY DESIGN: Medical record abstraction. METHODS: Utilizing an international, multi-institutional collaborative, we collected retrospective data on patient characteristics, treatment, and clinical outcomes. We investigated variation between and within open and endoscopic treatment approaches and assessed therapeutic outcomes; specifically, disease recurrence and need for tracheostomy at last follow-up. RESULTS: Strikingly, 479 iSGS patients across 10 participating centers were nearly exclusively female (98%, 95% confidence interval [CI], 96.1-99.6), Caucasian (95%, 95% CI, 92.2-98.8), and otherwise healthy (mean age-adjusted Charlson Comorbidity Index 1.5; 95% CI, 1.44-1.69). The patients presented at a mean age of 50 years (95% CI, 48.8-51.1). A total of 80.2% were managed endoscopically, whereas 19.8% underwent open reconstruction. Endoscopic surgery had a significantly higher rate of disease recurrence than the open approach (chi2 = 4.09, P = 0.043). Tracheostomy was avoided in 97% of patients irrespective of surgical

approach (95% CI, 94.5-99.8). Interestingly, there were outliers in rates of disease recurrence between centers using similar treatment approaches. CONCLUSION: Idiopathic subglottic stenosis patients are surprisingly homogeneous. The heterogeneity of treatment approaches and the observed outliers in disease recurrence rates between centers raises the potential for improved clinical outcomes through a detailed understanding of the processes of care. LEVEL OF EVIDENCE: 4. Laryngoscope, 2015.

Gelfer, G., Perry, L., & Deodhar, A. (2015). Golimumab for the treatment of axial spondyloarthritis. *Expert Review of Clinical Immunology,*

Axial spondyloarthritis (axSpA) is a chronic, immune-mediated inflammatory disease of the axial skeleton that includes ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Patients with AS experience chronic pain due to sacroiliac joint and spinal inflammation, and may develop spinal ankylosing with syndesmophyte formation. Tumor necrosis factor α inhibitors (TNFi) have shown promise in the management of AS and axSpA by targeting the underlying inflammatory process, and providing symptomatic relief. Whether they alter the progression of the disease is uncertain. Golimumab is a fully human IgG1 monoclonal antibody that targets and downregulates the pro-inflammatory cytokine TNF-α. The use of golimumab has been shown to reduce the signs and symptoms of axSpA as well as improve patient function and quality reported outcomes. This review focuses on the biological rationale and the results of clinical trials with golimumab for the treatment of axSpA. © 2015 Taylor & Francis

Gelfer, G., Perry, L., & Deodhar, A. (2016). Golimumab for the treatment of axial spondyloarthritis. *Expert Review of Clinical Immunology, 12*(1), 9-18.

Axial spondyloarthritis (axSpA) is a chronic, immune-mediated inflammatory disease of the axial skeleton that includes ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Patients with AS experience chronic pain due to sacroiliac joint and spinal inflammation, and may develop spinal ankylosing with syndesmophyte formation. Tumor necrosis factor alpha inhibitors (TNFi) have shown promise in the management of AS and axSpA by targeting the underlying inflammatory process, and providing symptomatic relief. Whether they alter the progression of the disease is uncertain. Golimumab is a fully human IgG1 monoclonal

antibody that targets and downregulates the pro-inflammatory cytokine TNF-alpha. The use of golimumab has been shown to reduce the signs and symptoms of axSpA as well as improve patient function and quality reported outcomes. This review focuses on the biological rationale and the results of clinical trials with golimumab for the treatment of axSpA.

German, D. M., Kabir, M. M., Dewland, T. A., Henrikson, C. A., & Tereshchenko, L. G. (2015). Atrial fibrillation predictors: Importance of the electrocardiogram. *Annals of Noninvasive Electrocardiology : The Official Journal of the International Society for Holter and Noninvasive Electrocardiology, Inc,*

Atrial fibrillation (AF) is the most common arrhythmia in adults and is associated with significant morbidity and mortality. Substantial interest has developed in the primary prevention of AF, and thus the identification of individuals at risk for developing AF. The electrocardiogram (ECG) provides a wealth of information, which is of value in predicting incident AF. The PR interval and P wave indices (including P wave duration, P wave terminal force, P wave axis, and other measures of P wave morphology) are discussed with regard to their ability to predict and characterize AF risk in the general population. The predictive value of the QT interval, ECG criteria for left ventricular hypertrophy, and findings of atrial and ventricular ectopy are also discussed. Efforts are underway to develop models that predict AF incidence in the general population; however, at present, little information from the ECG is included in these models. The ECG provides a great deal of information on AF risk and has the potential to contribute substantially to AF risk estimation, but more research is needed.

Gesuete, R., Christensen, S. N., Bahjat, F. R., Packard, A. E., Stevens, S. L., Liu, M., et al. (2015). Cytosolic receptor melanoma differentiation-associated protein 5 mediates preconditioning-induced neuroprotection against cerebral ischemic injury. *Stroke; a Journal of Cerebral Circulation,*

BACKGROUND AND PURPOSE: Preconditioning with poly-l-lysine and carboxymethylcellulose (ICLC) provides robust neuroprotection from cerebral ischemia in a mouse stroke model. However, the receptor that mediates neuroprotection is unknown. As a synthetic double-stranded RNA, poly-ICLC may bind endosomal Toll-like receptor 3 or one of the cytosolic retinoic acid-

inducible gene-I-like receptor family members, retinoic acid-inducible gene-I, or melanoma differentiation-associated protein 5. Activation of these receptors culminates in type I interferons (IFN-alpha/beta) induction-a response required for poly-ICLC-induced neuroprotection. In this study, we investigate the receptor required for poly-ICLC-induced neuroprotection. METHODS: Toll-like receptor 3, melanoma differentiation-associated protein 5-, and IFN-promoter stimulator 1-deficient mice were treated with poly-ICLC 24 hours before middle cerebral artery occlusion. Infarct volume was measured 24 hours after stroke to identify the receptor signaling pathways involved in protection. IFN-alpha/beta induction was measured in plasma samples collected 6 hours after poly-ICLC treatment. IFN-beta-deficient mice were used to test the requirement of IFN-beta for poly-ICLC-induced neuroprotection. Mice were treated with recombinant IFN-alpha-A to test the role of IFN-alpha as a potential mediator of neuroprotection. RESULTS: Poly-ICLC induction of both neuroprotection and systemic IFN-alpha/beta requires the cytosolic receptor melanoma differentiation-associated protein 5 and the adapter molecule IFN-promoter stimulator 1, whereas it is independent of Toll-like receptor 3. IFN-beta is not required for poly-ICLC-induced neuroprotection. IFN-alpha treatment protects against stroke. CONCLUSIONS: Poly-ICLC preconditioning is mediated by melanoma differentiation-associated protein 5 and its adaptor molecule IFN-promoter stimulator 1. This is the first evidence that a cytosolic receptor can mediate neuroprotection, providing a new target for the development of therapeutic agents to protect the brain from ischemic injury.

Ghani, M., Reitz, C., Cheng, R., Vardarajan, B. N., Jun, G., Sato, C., et al. (2015). Association of long runs of homozygosity with alzheimer disease among african american individuals. *JAMA Neurology, 72*(11), 1313-1323.

IMPORTANCE: Mutations in known causal Alzheimer disease (AD) genes account for only 1% to 3%of patients and almost all are dominantly inherited. Recessive inheritance of complex phenotypes can be linked to long (>1-megabase [Mb]) runs of homozygosity (ROHs) detectable by single-nucleotide polymorphism (SNP) arrays. OBJECTIVE: To evaluate the association between ROHs and AD in an African American population known to have a risk for AD up to 3 times higher than white individuals. DESIGN, SETTING, AND PARTICIPANTS: Case-control study of a large African American data set previously genotyped on different genome-wide SNP arrays

conducted from December 2013 to January 2015. Global and locus-basedROHmeasurementswere analyzed using rawor imputed genotype data.We studied the rawgenotypes from 2 case-control subsets grouped based on SNP array: Alzheimer's Disease Genetics Consortium data set (871 cases and 1620control individuals) and Chicago Health and Aging Project-Indianapolis Ibadan Dementia Study data set (279 cases and 1367 control individuals).We then examined the entire data set using imputed genotypes from 1917 cases and 3858 control individuals. MAIN OUTCOMES AND MEASURES: The ROHs larger than 1Mb, 2Mb, or 3Mb were investigated separately for global burden evaluation, consensus regions, and gene-based analyses. RESULTS: The African American cohort had a lowdegree of inbreeding (F × 0.006). In the Alzheimer's Disease Genetics Consortium data set, we detected a significantly higher proportion of cases with ROHs greater than 2Mb (P =.004) or greater than 3Mb (P =.02), aswell as a significant 114-kilobase consensus region on chr4q31.3 (empirical P value 2 =.04; ROHs >2 Mb). In the Chicago Health and Aging Project-Indianapolis Ibadan Dementia Study data set, we identified a significant 202-kilobase consensus region on Chr15q24.1 (empirical P value 2 =.02; ROHs >1 Mb) and a cluster of 13 significant genes on Chr3p21.31 (empirical P value 2 =.03; ROHs >3 Mb). Atotal of 43 of 49 nominally significant genescommonfor both data sets also mapped to Chr3p21.31. Analyses of imputed SNP data from the entire data set confirmed the association of AD with global ROH measurements (12.38 ROHs >1Mb in cases vs 12.11 in controls; 2.986Mb average size of ROHs >2Mb in cases vs 2.889Mb in controls; and 22%of cases with ROHs >3Mb vs 19% of controls) and a gene-cluster on Chr3p21.31 (empirical P value 2 =.006-.04; ROHs >3 Mb). Also, we detected a significant association between AD and CLDN17 (empirical P value 2 =.01; ROHs >1 Mb), encoding a protein from the Claudin family, members of whichwere previously suggested as ADbiomarkers. CONCLUSIONS AND RELEVANCE: To our knowledge, we discovered the first evidence of increased burden of ROHs among patients with AD from an outbred African American population, which could reflect either the cumulative effect of multiple ROHs to AD or the contribution of specific loci harboring recessive mutations and risk haplotypes in a subset of patients. Sequencing is required to uncover AD variants in these individuals.

Goeres, L. M., Gille, A., Furuno, J. P., Erten-Lyons, D., Hartung, D. M., Calvert, J. F., et al. (2015). Rural-urban differences in chronic disease and drug utilization in older oregonians. *The Journal of Rural Health : Official Journal of the American Rural Health Association and the National Rural Health Care Association,*

PURPOSE: To characterize disease burden and medication usage in rural and urban adults aged >/=85 years. METHODS: This is a secondary analysis of 5 years of longitudinal data starting in the year 2000 from 3 brain-aging studies. Cohorts consisted of community-dwelling adults: 1 rural cohort, the Klamath Exceptional Aging Project (KEAP), was compared to 2 urban cohorts, the Oregon Brain Aging Study (OBAS) and the Dementia Prevention study (DPS). In this analysis, 121 participants were included from OBAS/DPS and 175 participants were included from KEAP. Eligibility was determined based on age >/=85 years and having at least 2 follow-up visits after the year 2000. Disease burden was measured by the Modified Cumulative Illness Rating Scale (MCIRS), with higher values representing more disease. Medication usage was measured by the estimated mean number of medications used by each cohort. FINDINGS: Rural participants had significantly higher disease burden as measured by MCIRS, 23.0 (95% CI: 22.3-23.6), than urban participants, 21.0 (95% CI: 20.2-21.7), at baseline. The rate of disease accumulation was a 0.2 increase in MCIRS per year (95% CI: 0.05-0.34) in the rural population. Rural participants used a higher mean number of medications, 5.5 (95% CI: 4.8-6.1), than urban participants, 3.7 (95% CI: 3.1-4.2), at baseline (P /=85 years may differ by disease burden and medication usage. Future research should identify opportunities to improve health care for older adults.

Golden, D. W., Braunstein, S., Jimenez, R. B., Mohindra, P., Spektor, A., Ye, J. C., et al. (2015). Multi-institutional implementation and evaluation of a curriculum for the medical student clerkship in radiation oncology. *Journal of the American College of Radiology,*

Purpose: Radiation oncology curriculum development is challenging because of limited numbers of trainees at any single institution. The goal of this project is to implement and evaluate a standardized medical student clerkship curriculum following the multi-institutional cooperative group research model. Methods: During the 2013 academic year, a standardized curriculum was implemented at 11 academic medical centers consisting of three 1-hour lectures and a hands-on radiation treatment planning workshop. After the curriculum, students completed anonymous

evaluations using Likert-type scales (1 = "not at all" to 5 = "extremely") and free responses. Evaluations asked students to rate their comfort, before and after the curriculum, with radiation oncology as a specialty, knowledge of radiotherapy planning methods, and ability to function as a radiation oncology resident. Nonparametric statistical tests were used in the analysis. Results: Eighty-eight students at 11 academic medical centers completed the curriculum de novo, with a 72.7% (64 of 88) survey response rate. Fifty-seven students (89.1%) reported intent to pursue radiation oncology as their specialty. Median (interquartile range) student ratings of the importance of curricular content were as follows: overview, 4 (4-5); radiation biology/physics, 5 (4-5); practical aspects/emergencies, 5 (4-5); and planning workshop, 4 (4-5). Students reported that the curriculum helped them better understand radiation oncology as a specialty (5 [4-5]), increased specialty decision comfort (4 [3-5]), and would help the transition to radiation oncology residency (4 [4-5]). Students rated their specialty decision comfort significantly higher after completing the curriculum (4 [4-5] versus 5 [5-5]; $P < .001$). Conclusions: A national standardized curriculum was successfully implemented at 11 academic medical centers, providing proof of principle that curriculum development can follow the multi-institutional cooperative group research model. © 2015 American College of Radiology.

Gonçalves, L. M., Moreira, M. M., Azevedo, C. F., Valente, I. M., Sousa, J. C., Scanlan, T. S., et al. (2014). Proof of concept of the electrochemical sensing of 3-iodothyronamine (T1AM) and thyronamine (T0AM). *Chemelectrochem, 1*(10), 1623-1626.

Recent studies have shown that, besides the well-recognized T3 and T4 hormones, there are other relevant thyroid hormones circulating in the human body. In particular, this is the case for 3-iodothyronamine (T1AM) and thyronamine (T0AM). One of the reasons for the lack of studies showing their precise importance is the absence of analytical methodologies available. Herein, for the first time, T1AM and T0AM are electrochemically characterized. T0AM was sensed by means of a glassy carbon electrode; furthermore, T1AM was sensed both with a graphitic surface (oxidatively) as well as with mercury (reductively). For both compounds, after oxidation, it was possible to observe the reversible redox reaction concerning the benzoquinone/hydroquinone couple, thus increasing the specificity of the electroanalysis. Therefore, this work provides the

basis for an 'at-point-of-use' electrochemical strip test for T1AM and T0AM. © 2014 WILEY-VCH
Verlag GmbH & Co. KGaA, Weinheim.

Graff, J. N., Baciarello, G., Armstrong, A. J., Higano, C. S., Iversen, P., Flaig, T. W., et al. (2015).
Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive
metastatic castration-resistant prostate cancer: Results from PREVAIL. *Annals of Oncology :
Official Journal of the European Society for Medical Oncology / ESMO,*
BACKGROUND: Prostate cancer disproportionately affects older men. Because age affects
treatment decisions, it is important to understand the efficacy and tolerability of therapies for
advanced prostate cancer in elderly men. This analysis describes efficacy and safety outcomes in
men aged >/=75 years who received enzalutamide, an androgen receptor inhibitor, in the phase
III PREVAIL trial. PATIENTS AND METHODS: PREVAIL was a randomised, double-blind,
multinational study of oral enzalutamide 160 mg/day (N=872) versus placebo (N=845) in
chemotherapy-naive men with metastatic castration-resistant prostate cancer. Overall survival
(OS) and radiographic progression-free survival (rPFS) were coprimary endpoints. Subgroup
analysis of men aged >/=75 years ("elderly") and men aged <75 years was prespecified for the
coprimary endpoints and adverse events (AEs). RESULTS: Among 609 elderly patients (35%)
who participated in PREVAIL, median treatment duration was 16.6 and 5.0 months in the
enzalutamide and placebo arms, respectively. In the elderly subgroup, OS was greater with
enzalutamide than with placebo (32.4 months [95% CI 27.7-not yet reached] versus 25.1
months [95% CI 22.6-28.0]; hazard ratio [HR]=0.61 [95% CI 0.47-0.79]; P=0.0001), as was
rPFS (not yet reached [95% CI 12.3-not yet reached] versus 3.7 months [95% CI 3.6-5.3];
HR=0.17 [95% CI 0.12-0.24]; P<0.0001). Irrespective of treatment assignment, incidence of
AEs was similar between the two age groups, except for an overall higher incidence of falls
among elderly patients than younger patients (84/609 [13.8%] versus 62/1106 [5.6%]) and
among elderly patients receiving enzalutamide than those receiving placebo (61/317 [19.2%]
versus 23/292 [7.9%]). CONCLUSIONS: Elderly men benefited from treatment with enzalutamide
in terms of OS and rPFS. Enzalutamide was well tolerated in the elderly subgroup and those aged
<75 years. Age and enzalutamide treatment were associated with a higher incidence of falls.
CLINICAL TRIAL IDENTIFIER: NCT01212991, ClinicalTrials.gov.

Gray, J. W., & Mills, G. B. (2015). Large-scale drug screens support precision medicine. *Cancer Discovery, 5*(11), 1130-1132.

The major challenge underlying the emerging precision medicine initiative is to make links between cancer subsets and drugs that can be used to guide treatment of individual patients, leading to improved outcomes and decreased toxicity. Seashore-Ludlow and colleagues support this effort by reporting measurements of responses of 664 adherent cancer cell lines to 70 FDA-approved drugs, 100 experimental compounds, and 311 small-molecule probes. They use a novel Annotated Cluster Multidimensional Enrichment algorithm to identify drug mechanisms of action, molecular markers of response, responsive cancer subtypes, and compounds that produce synergistic cell inhibition. Cancer Discov; 5(11); 1130-2. (c)2015 AACR.See related article by Seashore-Ludlow et al., p. 1210.

Greenberg, R. G., Cochran, K. M., Smith, P. B., Edson, B. S., Schulman, J., Lee, H. C., et al. (2015). Effect of catheter dwell time on risk of central line-associated bloodstream infection in infants. *Pediatrics, 136*(6), 1080-1086.

BACKGROUND AND OBJECTIVE: Central venous catheters in the NICU are associated with significant morbidity and mortality because of the risk of central line-associated bloodstream infections (CLABSIs). The purpose of this study was to determine the effect of catheter dwell time on risk of CLABSI. METHODS: Retrospective cohort study of 13 327 infants with 15 567 catheters (93% peripherally inserted central catheters [PICCs], 7% tunneled catheters) and 256 088 catheter days cared for in 141 NICUs. CLABSI was defined using National Health Surveillance Network criteria. We defined dwell time as the number of days from line insertion until either line removal or day of CLABSI. We generated survival curves for each week of dwell time and estimated hazard ratios for CLABSI at each week by using a Cox proportional hazards frailty model. We controlled for postmenstrual age and year, included facility as a random effect, and generated separate models by line type. RESULTS: Median postmenstrual age was 29 weeks (interquartile range 26-33). The overall incidence of CLABSI was 0.93 per 1000 catheter days. Increased dwell time was not associated with increased risk of CLABSI for PICCs. For tunneled catheters, infection incidence was significantly higher in weeks 7 and 9 compared with week 1. CONCLUSIONS: Clinicians should not routinely replace uninfected PICCs for fear of infection but

should consider removing tunneled catheters before week 7 if no longer needed. Additional studies are needed to determine what daily maintenance practices may be associated with decreased risk of infection, especially for tunneled catheters.

Gregorovic, G., Boulden, E. A., Bosshard, R., Karstegl, C. E., Skalsky, R., Cullen, B. R., et al. (2015). Epstein-barr viruses (EBVs) deficient in EBV-encoded RNAs have higher levels of latent membrane protein 2 RNA expression in lymphoblastoid cell lines and efficiently establish persistent infections in humanized mice. *Journal of Virology, 89*(22), 11711-11714. Functions of Epstein-Barr virus (EBV)-encoded RNAs (EBERs) were tested in lymphoblastoid cell lines containing EBER mutants of EBV. Binding of EBER1 to ribosomal protein L22 (RPL22) was confirmed. Deletion of EBER1 or EBER2 correlated with increased levels of cytoplasmic EBV LMP2 RNA and with small effects on specific cellular microRNA (miRNA) levels, but protein levels of LMP1 and LMP2A were not affected. Wild-type EBV and EBER deletion EBV had approximately equal abilities to infect immunodeficient mice reconstituted with a human hematopoietic system. © 2015, American Society for Microbiology.

Griffith-Bauer, K., Leitenberger, S. L., & Krol, A. (2015). Febrile ulceronecrotic mucha-habermann disease: Two cases with excellent response to methotrexate. *Pediatric Dermatology,* Febrile ulceronecrotic Mucha-Habermann disease (FUMHD), a severe form of pityriasis lichenoides et varioliformis acuta (PLEVA), featuring large, ulcerative, necrotic skin plaques, high fever, and other systemic symptoms, is a rare disorder of unknown etiology. No randomized controlled trials have established treatment guidelines and multiple modalities are often employed, making it difficult to assess the efficacy of any single agent. We report two cases of this condition in which treatment with methotrexate plus antibiotic treatment for superinfection led to rapid improvement. © 2015 Wiley Periodicals, Inc.

Griglock, T. M., Sinclair, L., Mench, A., Cormack, B., Bidari, S., Rill, L., et al. (2015). Determining organ doses from CT with direct measurements in postmortem subjects: Part 1-methodology and validation. *Radiology, 277*(2), 463-470. Purpose: To develop a methodology that allows direct measurement of organ doses from computed tomographic (CT) examinations of postmortem subjects. Materials and Methods: In

this institutional review board approved study, the X-ray linear attenuation coefficients of various tissues were calculated from the mean CT numbers of images that were obtained in eight embalmed adult female cadavers and compared with the corresponding linear attenuation coefficients calculated from CT images obtained in eight living patients that were body mass index (BMI)-matched. Dosimetry was performed in three of the cadavers by accessing organs of interest and affixing partially sealed vinyl tubes inside them. Optically stimulated luminescent dosimeters (OSLDs) were inserted into the tubes and positioned within the organs of interest and on the skin. OSLDs were read with an InLight MicroStar (Landauer, Glenwood, Ill) reader, and readings were corrected for energy and scatter response. Fifteen tubes containing dosimeters were used, and imaging was repeated twice in each cadaver, for a total of five standard clinical protocols. Average dosimetry values were used for analysis. Results: Differences in linear attenuation coefficients between living and embalmed cadaveric tissues were within 3% for the tissues investigated. Measured organ doses for a chest-abdomen-pelvis CT protocol were less than 32 mGy for all organs measured. Organs that were completely irradiated during a given examination received similar doses, whereas organs that were partially irradiated displayed a large variation in measured organ dose. Conclusion: The anatomic and radiation attenuation characteristics of cadavers are comparable to those of living human tissue. This methodology allows direct measurement of organ doses from clinical CT examinations. © 2015 RSNA.

Guinney, J., Dienstmann, R., Wang, X., De Reyniès, A., Schlicker, A., Soneson, C., et al. (2015). The consensus molecular subtypes of colorectal cancer. *Nature Medicine, 21*(11), 1350-1356. Colorectal cancer (CRC) is a frequently lethal disease with heterogeneous outcomes and drug responses. To resolve inconsistencies among the reported gene expression-based CRC classifications and facilitate clinical translation, we formed an international consortium dedicated to large-scale data sharing and analytics across expert groups. We show marked interconnectivity between six independent classification systems coalescing into four consensus molecular subtypes (CMSs) with distinguishing features: CMS1 (microsatellite instability immune, 14%), hypermutated, microsatellite unstable and strong immune activation; CMS2 (canonical, 37%), epithelial, marked WNT and MYC signaling activation; CMS3 (metabolic, 13%), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal, 23%), prominent transforming

growth factor-β activation, stromal invasion and angiogenesis. Samples with mixed features (13%) possibly represent a transition phenotype or intratumoral heterogeneity. We consider the CMS groups the most robust classification system currently available for CRC - with clear biological interpretability - and the basis for future clinical stratification and subtype-based targeted interventions. © 2015 Nature America, Inc.

Hall, T. A., Steiner, R. D., Wright, H., Wilmot, B., Roullet, J. -., Peters, M., et al. (2015). Lipid and sterol gene sequence variation in autism and correlates with neurodevelopmental status: A pilot study. *New Horizons in Translational Medicine, 2*(6-7), 137-146.

Objective: Research has uncovered potential links between lipid and sterol metabolism and autism spectrum disorder (ASD). We worked to characterize genetic sequence variants in lipid/sterol related genes in children affected with ASD to investigate the association between lipid/sterol gene sequence variation and neurodevelopmental phenotype that could identify new etiologies for ASD and eventually aid to focus intervention strategies. Design and methods: Children with confirmed ASD were recruited from a regional academic health center. Participants included 24 children (20 male and 4 female) between the ages of 40 to 81 months (M=60 months). Several neurodevelopmental measures were administered which provided an assessment of neurodevelopmental functional status. We applied our exome sequencing workflow to perform alignment to the Human Reference Sequence (build 37) base calling for every base pair in the reads that align to the reference sequence QC evaluation of the annotation of all genetic variants different from the reference sequence using dbSNP and the 1000 Genomes databases. We investigated whether novel variants identified were related to neurodevelopmental functioning. Results and conclusions: Variants occurred in 355 total genomic positions, 53 of which were not previously annotated as variant positions in either dbSNP or the 1000 Genomes Project's variant annotation. Of these 355 variants, 169 were nonsynonymous (31 were novel). The total number of variants observed in the exons of captured regions of an individual participant ranged from 88 to 117; novel variants ranged from four to 10 per participant, while nonsynonymous variants ranged from 36 and 51 per participant. The total number of nonsynonymous variants per subject was significantly associated with neurodevelopmental function. Further, several genes involved in sterol and lipid metabolism including NPC1, DHCR24

and others that when mutated cause diseases with ASD characteristics, were associated with ASD in Network analysis. Altogether, the findings suggest that nonsynonymous variants in lipid/sterol related genes may be a biological marker of neurodevelopment status in ASD. Results support an association between lipid and sterol metabolism and ASD and suggest the need for further research attempting to elucidate the mechanisms behind the association and the etiology and neurodevelopmental effects of ASD. Focal points: •BedsideUnderstanding the association between genetics and metabolism and ASD will contribute to the scientific understanding of complex neurodevelopmental disorders. Continued study into the association between lipid and sterol genes and ASD may lead to new novel and effective treatment options for ASD.•BenchsideA large number of genetic sequence variations are associated with ASD. Additional research is still needed to determine which associations contribute to various subtypes of ASD presentations, and to elucidate the mechanisms behind the observed association.•IndustryThe discovery of new genetically influenced ASD subtypes may lead to the development of new novel and effective treatment options for ASD.•CommunityThe development of new novel and effective treatment options for ASD will have a great impact on the quality of life of those impacted by ASD.•Regulatory agenciesSince the development of new novel and effective treatment options for ASD based on genetic substrates of the condition needs extensive support from the authorities for success in clinical translation, ongoing financial investments will be necessary to translate the research in the lab to the bedside. The governmental support can also help to minimize the associated costs of treating ASD overtime. © 2015 European Society for Translational Medicine.

Haran, F. J., Slaboda, J. C., King, L. A., Wright, W. G., Houlihan, D., & Norris, J. N. (2015). Sensitivity of the balance error scoring system and the sensory organization test in the combat environment. *Journal of Neurotrauma,*

This study evaluated the utility of the Balance Error Scoring System (BESS) and the Sensory Organization Test (SOT) as tools for the screening and monitoring of Service members (SMs) with mTBI in a deployed setting during the acute and sub-acute phases of recovery. Patient records (N=699) were reviewed for a cohort of SMs who sustained a blast-related mTBI while deployed to Afghanistan and were treated at the Concussion Restoration Care Center (CRCC) at

Camp Leatherneck. Upon initial intake into the CRCC participants completed two assessments of postural control, the BESS and SOT. SMs with mTBI performed significantly worse on the BESS and SOT when compared to comparative samples. When the SOT data was further examined using sensory ratios, the results indicated that postural instability was primarily a result of vestibular and visual integration dysfunction ($r > 0.62$). The main finding of this study was that the sensitivity of the SOT composite score (50-58%) during the acute phase was higher than previous sensitivities found in the sports medicine literature for impact-related trauma.

Harris, M. A., Wagner, D. V., Wilson, A. C., Spiro, K., Heywood, M., & Hoehn, D. (2015). Novel interventions in children's healthcare for youth hospitalized for chronic pain. *Clinical Practice in Pediatric Psychology, 3*(1), 48-58.

The purpose of this study was to pilot the implementation of the Novel Interventions in Children's Healthcare (NICH) program for youth with chronic pain who utilized a disproportionate amount of health care. Three youth (2 males and 1 female, aged 11 to 15 years) participated. The intervention consisted of a combination of family-based problem-solving, care coordination, and case management, with the inclusion of technology-assisted treatment delivery (e.g., text messages, video chat) to reduce costs. Both objective (i.e., hospitalization records) and subjective (e.g., interventionist reports) outcomes were examined to assess changes over the course of treatment. Two of the three youth demonstrated reductions in the number of days hospitalized and associated costs. In addition, interventionist reports indicated improved quality of life for family and youth served. Although further research is needed, NICH appears to be a promising intervention for youth with chronic pain and high health care utilization and shows the potential to result in improved youth health and reduced monetary costs for families, providers, and the healthcare system.

Heckman, T. G., Heckman, B. D., Anderson, T., Bianco, J. A., Sutton, M., & Lovejoy, T. I. (2015). Common factors and depressive symptom relief trajectories in group teletherapy for persons ageing with HIV. *Clinical Psychology & Psychotherapy,*

Telepsychology research has focused primarily on treatment efficacy, with far less attention devoted to how common factors relate to teletherapy outcomes. This research identified

trajectories of depressive symptom relief in 105 older people living with HIV with elevated depressive symptoms enrolled in a randomized clinical trial testing two 12-session group teletherapies and compared common factors (e.g., therapeutic alliance and group cohesion) across depressive symptom trajectory groups. Growth mixture modelling of weekly depression scores identified three depressive symptom change groups: (1) 'early improvers' (31%) who reported reductions in depressive symptoms by Session 4; (2) 'delayed improvers' (16%) whose symptoms improved after Session 5 and (3) 'non-improvers' (53%). Therapeutic alliance was unrelated to treatment outcome group. Group cohesion was greater in early improvers than non-improvers. Group cohesion was unexpectedly lower, and group member similarity was greater in delayed improvers than non-improvers. Early improvers had been living with HIV/AIDS for fewer years than non-improvers. In group teletherapy, group cohesion and group member similarity are more important than client-therapist alliance. Copyright (c) 2015 John Wiley & Sons, Ltd. KEY PRACTITIONER MESSAGE: In group teletherapy with older people living with HIV (OPLWHIV), three latent outcome trajectory groups emerged over the 12-week treatment period: (1) non-improvers (53%); (2) early improvers (31%) and (3) delayed improvers (16%). In group teletherapy with OPLWHIV, group cohesion is a stronger predictor of depressive symptom relief than is client-therapist alliance. OPLWHIV in group teletherapy who do not respond to treatment until the latter therapy sessions can still experience depressive symptom relief comparable with early responders.

Hill, A. P., Zuckerman, K. E., & Fombonne, E. (2015). Obesity and autism. *Pediatrics, 136*(6), 1051-1061.

OBJECTIVE: Overweight and obesity are increasingly prevalent in the general pediatric population. Evidence suggests that children with autism spectrum disorders (ASDs) may be at elevated risk for unhealthy weight. We identify the prevalence of overweight and obesity in a multisite clinical sample of children with ASDs and explore concurrent associations with variables identified as risk factors for unhealthy weight in the general population. METHODS: Participants were 5053 children with confirmed diagnosis of ASD in the Autism Speaks Autism Treatment Network. Measured values for weight and height were used to calculate BMI percentiles; Centers for Disease Control and Prevention criteria for BMI for gender and age were used to define

overweight and obesity (>/=85th and >/=95th percentiles, respectively). RESULTS: In children age 2 to 17 years, 33.6% were overweight and 18% were obese. Compared with a general US population sample, rates of unhealthy weight were significantly higher among children with ASDs ages 2 to 5 years and among those of non-Hispanic white origin. Multivariate analyses revealed that older age, Hispanic or Latino ethnicity, lower parent education levels, and sleep and affective problems were all significant predictors of obesity. CONCLUSIONS: Our results indicate that the prevalence of unhealthy weight is significantly greater among children with ASD compared with the general population, with differences present as early as ages 2 to 5 years. Because obesity is more prevalent among older children in the general population, these findings raise the question of whether there are different trajectories of weight gain among children with ASDs, possibly beginning in early childhood.

Hofmann, M. E., & Andresen, M. C. (2016). Vanilloids selectively sensitize thermal glutamate release from TRPV1 expressing solitary tract afferents. *Neuropharmacology, 101*, 401-411. Vanilloids, high temperature, and low pH activate the transient receptor potential vanilloid type 1 (TRPV1) receptor. In spinal dorsal root ganglia, co-activation of one of these gating sites on TRPV1 sensitized receptor gating by other modes. Here in rat brainstem slices, we examined glutamate synaptic transmission in nucleus of the solitary tract (NTS) neurons where most cranial primary afferents express TRPV1, but TRPV1 sensitization is unknown. Electrical shocks to the solitary tract (ST) evoked EPSCs (ST-EPSCs). Activation of TRPV1 with capsaicin (100 nM) increased spontaneous EPSCs (sEPSCs) but inhibited ST-EPSCs. High concentrations of the ultra-potent vanilloid resiniferatoxin (RTX, 1 nM) similarly increased sEPSC rates but blocked ST-EPSCs. Lowering the RTX concentration to 150 pM modestly increased the frequency of the sEPSCs without causing failures in the evoked ST-EPSCs. The sEPSC rate increased with raising bath temperature to 36 °C. Such thermal responses were larger in 150 pM RTX, while the ST-EPSCs remained unaffected. Vanilloid sensitization of thermal responses persisted in TTX but was blocked by the TRPV1 antagonist capsazepine. Our results demonstrate that multimodal activation of TRPV1 facilitates sEPSC responses in more than the arithmetic sum of the two activators, i.e. co-activation sensitizes TRPV1 control of spontaneous glutamate release. Since action potential evoked glutamate release is unaltered, the work provides evidence for

cooperativity in gating TRPV1 plus a remarkable separation of calcium mechanisms governing the independent vesicle pools responsible for spontaneous and evoked release at primary afferents in the NTS. © 2015 Elsevier Ltd.

Hohlfelder, B., Stashek, C., Anger, K. E., & Szumita, P. M. (2016). Utilization of a pharmacy clinical surveillance system for pharmacist alerting and communication at a tertiary academic medical center. *Journal of Medical Systems, 40*(1), 24-015-0398-9. Epub 2015 Nov 7.
The objective of this analysis is to describe the utilization metrics of a pharmacy clinical surveillance system (PCSS) at a tertiary, academic medical center.We performed a retrospective database analysis assessing rule-based alerts (RBA), interventions and pharmacist communication notes documented in the PCSS from January 1, 2014 to December 31, 2014. Reports were generated on 92 unique RBAs sent to clinicians for evaluation. Metrics assessed included the number of RBAs that were triggered, clinically evaluated, intervened on by pharmacists, and therapeutic category of interventions. Pharmacy communication notes were also evaluated.A total of 399,979 RBAs were triggered through the PCSS. During that time, pharmacists documented a total of 17,733 interventions. The most common RBAs were related to lab abnormalities (132,487; 33 %) and anticoagulation/antiplatelet therapy (126,425; 32.1 %). Interventions were most frequently related to RBAs regarding anticoagulation/antiplatelet therapy (6412; 36 %) and antimicrobial therapy (3320; 19 %). Pharmacist communication was most commonly related to clarification of medication and lab orders, and therapeutic drug monitoring.Based on utilization metrics presented, the implementation of a PCSS has successfully generated RBAs to aid pharmacists in clinical practice and improved departmental documentation and communication. Further analysis is warranted to assess the impact of the RBAs, interventions, and communication notes on outcomes such as hospital cost and adverse drug events.

Hoorn, E. J., Loffing, J., & Ellison, D. H. (2015). An integrated view of potassium homeostasis. *New England Journal of Medicine, 373*(18), 1786.

Hoos, T., Warren, M., & Martindale, R. G. (2015). *Perioperative nutritional intervention: Where are we?* S. Karger AG.

As we look forward in 2015, attention to perioperative surgical nutrition continues to play a key role in optimizing outcomes and enhancing surgical recovery. Nutrition therapies for preoperative preparation include high protein intake combined with exercise, immune- and metabolic-modulating nutrients, carbohydrate loading, probiotic therapy and, occasionally, the need for specialized enteral or parenteral nutrition. Early enteral nutrition and probiotic therapy optimize gastrointestinal integrity and function in the postoperative setting. Some questions of who, when and how to optimally feed the surgical patient still exist. Despite these questions, the abundance of evidence supports a determined focus for nutrition optimization prior to major surgery. © 2015 Nestec Ltd., Vevey/S. Karger AG, Basel.

Horner-Johnson, W., Darney, B. G., Kulkarni-Rajasekhara, S., Quigley, B., & Caughey, A. B. (2015). Pregnancy among U.S. women: Differences by presence, type, and complexity of disability. *American Journal of Obstetrics and Gynecology,*

BACKGROUND: Approximately 12% of women of reproductive age have some type of disability. Very little is known about sexual and reproductive health issues among women with disabilities, including what proportion of women with disabilities experience pregnancy. Data on pregnancy are important to inform needs for preconception and pregnancy care for women with disabilities. OBJECTIVE: The purpose of this study was to describe the occurrence of pregnancy among women with various types of disability and with differing levels of disability complexity, compared to women without disabilities, in a nationally representative sample. STUDY DESIGN: We conducted cross-sectional analyses of 2008-2012 Medical Expenditure Panel Survey data to estimate the proportion of women ages 18-44 with and without disabilities who reported a pregnancy during their 2-year participation on the survey panel. We used multivariable logistic regression to test the association of pregnancy with presence, type, and complexity of disability, controlling for other factors associated with pregnancy. RESULTS: Similar proportions of women with and without disabilities reported a pregnancy (10.8% vs. 12.3%, with 95% confidence intervals overlapping). Women with the most complex disabilities (those that impact activities such as self-care and work) were less likely to have been pregnant (AOR=0.69, 95%CI=0.52-0.93), but women whose disabilities only affected basic actions (seeing, hearing, movement, cognition) did not differ significantly from women with no disabilities. CONCLUSION: Women with

a variety of types of disabilities experience pregnancy. Greater attention is needed to the reproductive healthcare needs of this population in order to ensure appropriate contraceptive, preconception, and perinatal care.

Hudgens, S., Pelletier, C., Forsythe, A., & Taylor, M. (2015). Capturing quality of life (qol) data in rare indications: Case study in radioiodine-refractory thyroid cancer (rr-dtc). *Value in Health : The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 18*(7), A726.

Huntington Study Group PHAROS Investigators, Biglan, K. M., Shoulson, I., Kieburtz, K., Oakes, D., Kayson, E., et al. (2015). Clinical-genetic associations in the prospective huntington at risk observational study (PHAROS): Implications for clinical trials. *JAMA Neurology,* , 1-9. Importance: Identifying measures that are associated with the cytosine-adenine-guanine (CAG) expansion in individuals before diagnosis of Huntington disease (HD) has implications for designing clinical trials. Objective: To identify the earliest features associated with the motor diagnosis of HD in the Prospective Huntington at Risk Observational Study (PHAROS). Design, Setting, and Participants: A prospective, multicenter, longitudinal cohort study was conducted at 43 US and Canadian Huntington Study Group research sites from July 9, 1999, through December 17, 2009. Participants included 983 unaffected adults at risk for HD who had chosen to remain unaware of their mutation status. Baseline comparability between CAG expansion (>/=37 repeats) and nonexpansion (<37 repeats) groups was assessed. All participants and investigators were blinded to individual CAG analysis. A repeated-measures analysis adjusting for age and sex was used to assess the divergence of the linear trend between the expanded and nonexpanded groups. Data were analyzed from April 27, 2010, to September 3, 2013. Exposure: Huntington disease mutation status in individuals with CAG expansion vs without CAG expansion. Main Outcomes and Measures: Unified Huntington's Disease Rating Scale motor (score range, 0-124; higher scores indicate greater impairment), cognitive (symbol digits modality is the total number of correct responses in 90 seconds; lower scores indicate greater impairment), behavioral (score range, 0-176; higher scores indicate greater behavioral symptoms), and functional (Total Functional Capacity score range, 0-13; lower scores indicate reduced functional ability) domains

were assessed at baseline and every 9 months up to a maximum of 10 years. Results: Among the 983 research participants at risk for HD in the longitudinal cohort, 345 (35.1%) carried the CAG expansion and 638 (64.9%) did not. The mean (SD) duration of follow-up was 5.8 (3.0) years. At baseline, participants with expansions had more impaired motor (3.0 [4.2] vs 1.9 [2.8]; P < .001), cognitive (P < .05 for all measures except Verbal Fluency, P = .52), and behavioral domain scores (9.4 [11.4] vs 6.5 [8.5]; P < .001) but not significantly different measures of functional capacity (12.9 [0.3] vs 13.0 [0.2]; P = .23). With findings reported as mean slope (95% CI), in the longitudinal analyses, participants with CAG expansions showed significant worsening in motor (0.84 [0.73 to 0.95] vs 0.03 [-0.05 to 0.11]), cognitive (-0.54 [-0.67 to -0.40] vs 0.22 [0.12 to 0.32]), and functional (-0.08 [-0.09 to -0.06] vs -0.01 [-0.02 to 0]) measures compared with those without expansion (P < .001 for all); behavioral domain scores did not diverge significantly between groups. Conclusions and Relevance: Using these prospectively accrued clinical data, relatively large treatment effects would be required to mount a randomized, placebo-controlled clinical trial involving premanifest HD individuals who carry the CAG expansion.

Jacob-Files, E., Rdesinski, R., Storey, M., Gipson, T., Cohen, D. J., Olds, D., et al. (2015). Should home-based contraceptive dispensing become a routine part of public health nurse practice? review of nurse perceptions. *Public Health Nursing, 32*(6), 702-710.

Objective: We examined public health nurses' beliefs about the safety of dispensing hormonal contraceptives in the home, the extent to which they considered contraceptive dispensing within their scope of practice, and the types of support needed to effectively dispense contraceptives in the home. Design and Sample: We conducted focus groups in Washington State with 24 home visiting nurses participating in a Nurse Family Partnership (NFP) randomized clinical trial in which nurses dispensed hormonal contraceptives during home visits. Measures: We assessed the feasibility of the intervention and barriers and facilitators to home dispensing of hormonal contraceptives. Results: Nurses were, on average 52 years old and had been working in nursing approximately 25 years, with between 5 and 18 years of experience working in a family planning setting. Overall, nurses believed that, with the right training and support, dispensing of hormonal contraceptives in the home was safe and fit within their scope of practice. Those nurses who

reported resistance to the intervention cited inadequate training, lack of clear protocols, and sufficient support as important deterrents. Conclusions: Home-based contraceptive dispensing by nurses is a feasible enhancement of the NFP program. To ensure that nurses are confident and able to dispense hormonal contraceptives, training, clinical protocols, consultation, and logistical support are needed. © 2015 Wiley Periodicals, Inc.

Jiang, J., Nguyen, T., & Rao, J. S. (2015). The E-MS algorithm: Model selection with incomplete data. *Journal of the American Statistical Association, 110*(511), 1136-1147.

We propose a procedure associated with the idea of the E-M algorithm for model selection in the presence of missing data. The idea extends the concept of parameters to include both the model and the parameters under the model, and thus allows the model to be part of the E-M iterations. We develop the procedure, known as the E-MS algorithm, under the assumption that the class of candidate models is finite. Some special cases of the procedure are considered, including E-MS with the generalized information criteria (GIC), and E-MS with the adaptive fence (AF; Jiang et al.). We prove numerical convergence of the E-MS algorithm as well as consistency in model selection of the limiting model of the E-MS convergence, for E-MS with GIC and E-MS with AF. We study the impact on model selection of different missing data mechanisms. Furthermore, we carry out extensive simulation studies on the finite-sample performance of the E-MS with comparisons to other procedures. The methodology is also illustrated on a real data analysis involving QTL mapping for an agricultural study on barley grains. Supplementary materials for this article are available online. © 2015, © American Statistical Association.

Kalenderian, E., Tokede, B., Ramoni, R., Khan, M., Kimmes, N., White, J., et al. (2015). Dental clinical research: An illustration of the value of standardized diagnostic terms. *Journal of Public Health Dentistry,*

OBJECTIVE: Secondary data are a significant resource for in-depth epidemiologic and public health research. It also allows for effective quality control and clinical outcomes measurement. To illustrate the value of structured diagnostic entry, a use case was developed to quantify adherence to current practice guidelines for managing chronic moderate periodontitis (CMP). METHODS: Six dental schools using the same electronic health record (EHR) contribute data to a

dental data repository (BigMouth) based on the i2b2 data-warehousing platform. Participating institutions are able to query across the full repository without being able to back trace specific data to its originating institution. At each of the three sites whose data are included in this analysis, the Dental Diagnostic System (DDS) terminology was used to document diagnoses in the clinics. We ran multiple queries against this multi-institutional database, and the output was validated by manually reviewing a subset of patient charts. RESULTS: Over the period under study, 1,866 patients were diagnosed with CMP. Of these, 15 percent received only periodontal prophylaxis treatment, 20 percent received only periodontal maintenance treatment, and only 41 percent received periodontal maintenance treatment in combination with other AAP guideline treatments. CONCLUSIONS: Our results showed that most patients with CMP were not treated according to the AAP guidelines. On the basis of this use case, we conclude that the availability and habitual use of a structured diagnosis in an EHR allow for the aggregation and secondary analyses of clinical data to support downstream analyses for quality improvement and epidemiological assessments.

Kansagara, D., Chiovaro, J. C., Kagen, D., Jencks, S., Rhyne, K., O'Neil, M., et al. (2015). So many options, where do we start? an overview of the care transitions literature. *Journal of Hospital Medicine,*

BACKGROUND: Health systems are faced with a large array of transitional care interventions and patient populations to whom such activities might apply. PURPOSE: To summarize the health and utilization effects of transitional care interventions, and to identify common themes about intervention types, patient populations, or settings that modify these effects. DATA SOURCES: PubMed and Cochrane Database of Systematic Reviews (January 1950-May 2014), reference lists, and technical advisors. STUDY SELECTION: Systematic reviews of transitional care interventions that reported hospital readmission as an outcome. DATA EXTRACTION: We extracted transitional care procedures, patient populations, settings, readmissions, and health outcomes. We identified commonalities and compiled a narrative synthesis of emerging themes. DATA SYNTHESIS: Among 10 reviews of mixed patient populations, there was consistent evidence that enhanced discharge planning and hospital-at-home interventions reduced readmissions. Among 7 reviews in specific patient populations, transitional care interventions

reduced readmission in patients with congestive heart failure and general medical populations. In general, interventions that reduced readmission addressed multiple aspects of the care transition, extended beyond hospital stay, and had the flexibility to accommodate individual patient needs. There was insufficient evidence on how caregiver involvement, transition to sites other than home, staffing, patient selection practices, or care settings modified intervention effects. CONCLUSIONS: Successful interventions are comprehensive, extend beyond hospital stay, and have the flexibility to respond to individual patient needs. The strength of evidence should be considered low because of heterogeneity in the interventions studied, patient populations, clinical settings, and implementation strategies. Journal of Hospital Medicine 2015. (c) 2015 Society of Hospital Medicine.

Kiage, J. N., Sampson, U. K., Lipworth, L., Fazio, S., Mensah, G. A., Yu, Q., et al. (2015). Polyunsaturated fat intake and mortality in non-statin users, is there an independent relationship? the authors reply. *Nutrition, Metabolism, and Cardiovascular Diseases : NMCD,*

Kim, A. J. H., & Warren, J. B. (2015). Optimal timing of umbilical cord clamping: Is the debate settled? part 1 of 2: History, rationale, influencing factors, and concerns. *Neoreviews, 16*(5), e263-e271.

In the middle of the 20th century, practices regarding the timing of umbilical cord clamping changed from delaying cord clamping to clamping the umbilical cord soon after delivery of the infant. In the last several years, interest in reviving delayed cord clamping has led to an abundance of literature on the subject. On the basis of recent research, many professional organizations in the fields of obstetrics, midwifery, and pediatrics have started to recommend the use of delayed cord clamping for at least a subset of infants. In part 1 of this 2-part review, we present the history of the delayed cord clamping debate, discuss the rationale behind the use of delayed cord clamping from a physiologic standpoint, detail the factors that affect transfusion volume during a delay in cord clamping, and examine the concerns that exist regarding the use of delayed cord clamping. In part 2, we present the evidence surrounding timing of cord clamping for the preterm and term infant and maternal outcomes. Finally, we discuss alternatives to

delayed cord clamping and present a summary of unanswered questions on the subject. © 2015 by the American Academy of Pediatrics. All rights reserved.

Kim, A. J. H., & Warren, J. B. (2015). Optimal timing of umbilical cord clamping: Is the debate settled? part 2 of 2: Evidence in preterm and term infants, alternatives, and unanswered questions. *Neoreviews, 16*(5), e270-e279.

In the middle of the 20th century, practices regarding the timing of umbilical cord clamping changed from delaying cord clamping to clamping the umbilical cord soon after delivery of the infant. In the last several years, interest in reviving delayed cord clamping has led to an abundance of literature on the subject. On the basis of recent research, many professional organizations in the fields of obstetrics, midwifery, and pediatrics have started to recommend the use of delayed cord clamping for at least a subset of infants. In part 1 of this 2-part review, we presented the history of the delayed cord clamping debate, discussed the rationale behind the use of delayed cord clamping from a physiologic standpoint, detailed the factors that affect transfusion volume during a delay in cord clamping, and examined the concerns that exist regarding the use of delayed cord clamping. In part 2, we present the evidence surrounding timing of cord clamping for the preterm and term infant and maternal outcomes. Finally, we discuss alternatives to delayed cord clamping and present a summary of unanswered questions on the subject. © 2015 by the American Academy of Pediatrics. All rights reserved.

Koba Bora, B., Lez, D. M., Luwa, D. O., Baguma, M. B., Katumbay, D. T., Kalula, T. K., et al. (2015). Living with epilepsy in lubumbashi (democratic republic of congo): Epidemiology, risk factors and treatment gap. *Pan African Medical Journal, 21*

Introduction: Epilepsy is the most common of serious neurological disorders, yet despite considerable efforts, good access to medication, appropriate social and societal acceptance and acceptable quality of life (QoL) are difficult to achieve especially in developing countries. It is estimated that over 500,000 people suffer from epilepsy in the DRC. There is no report, in our knowledge on the epilepsy in Lubumbashi. Methods: A descriptive study was undertaken in individuals with a clinical diagnosis of epilepsy who presented at the CNPJG outpatient clinic in Lubumbashi over a 12 months period. A 64-item questionnaire was used to collect information

from the patients. Case records were reviewed and relevant demographic, social, professional, medical history, medical condition data were extracted. Results: Among 3,540 patients who presented to a neuropsychiatric clinic run by the Fracarita charity over a 1-year period, 423 (11.9%) were identified as having epilepsy, and 179 were subsequently included in the survey after they (or their parent/guardian) provided informed consent and completed an EEG investigation. Data were collected using a standardized, 64-item questionnaire. Epilepsy had negative impact on the lives of individuals with the condition; 40.8% had either no education or had completed primary education only, 38.0% were unemployed and the majority (64.6%; n=113) were unmarried or divorced. Family history of epilepsy (first or second degree) was present in 23.5% of cases. Other reported factors that could potentially precipitate epilepsy included obstetric and perinatal factors (15.1%) and central nervous system infections during infancy (8.4%). Consumption of alcohol or recreational drugs accounted for 10.6%. The treatment gap was above 67% and the delay between first seizure and first consultation was 15 months. When asked to describe their condition, or its cause, 55.3% of participants (or their families) considered epilepsy to be of spiritual/religious origin, while 25.1% had almost no insight and could not provide any description. Conclusion: This first epidemiological study shows a high prevalence of epilepsy among patients presenting to the clinic in Lubumbashi, DRC, and reveals a significant treatment gap. © Béatrice Koba-Bora et al.

Kolivras, A., Andre, J., Thompson, C., Sass, U., & Fraitag, S. (2015). Pseudoangiomatous xanthelasmoid mastocytosis: Two case reports demonstrating the hypervascularity of this rare variant of cutaneous mastocytosis. *Journal of Cutaneous Pathology,*

Kugelman, T., Zuloaga, D. G., Weber, S., & Raber, J. (2015). Post-training gamma irradiation-enhanced contextual fear memory associated with reduced neuronal activation of the infralimbic cortex. *Behavioural Brain Research, 298*(Pt B), 1-11.
The brain might be exposed to irradiation under a variety of situations, including clinical treatments, nuclear accidents, dirty bomb scenarios, and military and space missions. Correctly recalling tasks learned prior to irradiation is important but little is known about post-learning effects of irradiation. It is not clear whether exposure to X-ray irradiation during memory

consolidation, a few hours following training, is associated with altered contextual fear conditioning 24h after irradiation and which brain region(s) might be involved in these effects. Brain immunoreactivity patterns of the immediately early gene c-Fos, a marker of cellular activity was used to determine which brain areas might be altered in post-training irradiation memory retention tasks. In this study, we show that post-training gamma irradiation exposure (1Gy) enhanced contextual fear memory 24h later and is associated with reduced cellular activation in the infralimbic cortex. Reduced GABA-ergic neurotransmission in parvalbumin-positive cells in the infralimbic cortex might play a role in this post-training radiation-enhanced contextual fear memory.

Kugelman, T., Zuloaga, D. G., Weber, S., & Raber, J. (2016). Post-training gamma irradiation-enhanced contextual fear memory associated with reduced neuronal activation of the infralimbic cortex. *Behavioural Brain Research, 298*, 1-11.
The brain might be exposed to irradiation under a variety of situations, including clinical treatments, nuclear accidents, dirty bomb scenarios, and military and space missions. Correctly recalling tasks learned prior to irradiation is important but little is known about post-learning effects of irradiation. It is not clear whether exposure to X-ray irradiation during memory consolidation, a few hours following training, is associated with altered contextual fear conditioning 24. h after irradiation and which brain region(s) might be involved in these effects. Brain immunoreactivity patterns of the immediately early gene c-Fos, a marker of cellular activity was used to determine which brain areas might be altered in post-training irradiation memory retention tasks. In this study, we show that post-training gamma irradiation exposure (1. Gy) enhanced contextual fear memory 24. h later and is associated with reduced cellular activation in the infralimbic cortex. Reduced GABA-ergic neurotransmission in parvalbumin-positive cells in the infralimbic cortex might play a role in this post-training radiation-enhanced contextual fear memory. © 2015 Elsevier B.V.

Kurz, M. C., Prince, D. K., Christenson, J., Carlson, J., Stub, D., Cheskes, S., et al. (2015). Association of advanced airway device with chest compression fraction during out-of-hospital cardiopulmonary arrest. *Resuscitation, 98*, 35-40.

BACKGROUND: Select Emergency Medical Services (EMS) practitioners substitute endotracheal intubation (ETI) with supraglottic airway (SGA) insertion to minimize CPR chest compression interruptions, but the resulting effects upon chest compression fraction (CCF) are unknown. We sought to determine the differences in CCF between adult out-of-hospital cardiac arrest (OHCA) receiving ETI and those receiving SGA. METHODS: We studied adult, non-traumatic OHCA patients enrolled in the Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation using an Impedance valve and an Early vs. Delayed analysis (PRIMED) trial. Chest compressions were measured using compression or thoracic impedance sensors. We limited the analysis to those receiving ETI or SGA (Combitube, King Laryngeal Tube, or Laryngeal Mask Airway) and >2min of chest compression data before and after airway insertion. We compared CCF between ETI and SGA before and after airway insertion, adjusting for age, sex, witnessed arrest, bystander CPR, shockable initial rhythm, public location, PRIMED trial arm, and regional ROC center. We also compared the change in CCF for each airway technique. RESULTS: Of 14,955 patients enrolled in the ROC PRIMED trial, we analyzed 2767 cases, including 2051 ETI, 671 SGA, and 45 both. Among subjects in this investigation the mean age was 66.4 years with a male predominace, 46% with witnessed event, 37% receiving bystander CPR, and 22% presenting with an initially shockable rhythm. Pre- and post-airway CCF was higher for SGA than ETI (SGA pre-airway CCF 73.2% [95%CI: 71.6-74.7%] vs. ETI 70.6% [95%CI: 69.7-71.5%]; post-airway 76.7% [95%CI: 75.2-78.1%] vs. 72.4% [95%CI: 71.5-73.3%]). After adjusting for potential confounders, these significant changes persisted (pre-airway difference 2.2% favoring SGA, p-value=0.046; post-airway 3.4% favoring SGA, p=0.001). CONCLUSION: In patients with OHCA, we detected a slightly higher rate of CCF in patients for whom a SGA was inserted, both before and after insertion. However, the actual differences were so small, that in the context of this observational, secondary analysis, it is unclear if this represents a clinically significant difference.

Lee, C. S. (2015). Mechanisms of cardiotoxicity and the development of heart failure. *Critical Care Nursing Clinics of North America, 27*(4), 469-481.

Cardiotoxicity is a broad term that refers to the negative effects of toxic substances on the heart. Cancer drugs can cause cardiotoxicity by effects on heart cells, thromboembolic events, and/or hypertension that can lead to heart failure. Rheumatoid arthritis biologics may interfere with

ischemic preconditioning and cause/worsen heart failure. Long-term and heavy alcohol use can result in oxidative stress, apoptosis, and decreased contractile protein function. Cocaine use results in sympathetic nervous system stimulation of heart and smooth muscle cells and leads to cardiotoxicity and evolution of heart failure. The definition of cardiotoxicity is likely to evolve along with knowledge about detecting subclinical myocardial injury.

Lee, C. S., Mudd, J. O., Hiatt, S. O., Gelow, J. M., Chien, C., & Riegel, B. (2015). Trajectories of heart failure self-care management and changes in quality of life. *European Journal of Cardiovascular Nursing, 14*(6), 486-494.

Introduction: Heart failure patients vary considerably in their self-care management behaviors (i.e. recognizing and responding to symptoms). The goal of this study was to identify unique patterns of change in heart failure self-care management and quantify associations between self-care management and quality of life (HRQOL) over time. Methods: A prospective cohort study among adults with symptomatic heart failure was designed to measure changes in self-care management (Self-care of Heart Failure Index) and HRQOL (Kansas City Cardiomyopathy Questionnaire) over six months. Growth mixture modeling was used to identify unique trajectories of change in self-care management. Results: The mean age (n=146) was 57 years, 70% were male, and 41% had class II heart failure. Two trajectories of self-care management were identified (entropy = 0.88). The larger trajectory (73.3%) was characterized by a significant decline in self-care management over time and no change in HRQOL. The smaller trajectory (26.7%) was characterized by marked improvements in self-care management and HRQOL. Changes in heart failure self-care management occurred in the absence of change in routine self-care maintenance behaviors, functional classification, and physical and psychological symptoms. Patients with greater physical symptoms at enrollment (odds ratio (OR) =1.04, p=0.037), larger left ventricles (OR=1.50, p=0.044), and ischemic heart failure (OR=3.84, p=0.014) were more likely to have the declining trajectory of self-care management. Higher levels of depression at enrollment were associated with reduced odds of having a decline in self-care management over time (OR=0.85, p<0.001). Conclusions: There are unique and clinically-relevant trajectories of change in heart failure self-care management that are associated with differences in HRQOL. © 2015 European Society of Cardiology.

Lipstein, E. A., Lindly, O. J., Anixt, J. S., Britto, M. T., & Zuckerman, K. E. (2015). Shared decision

making in the care of children with developmental and behavioral disorders. *Maternal and Child

Health Journal,*

Objective Shared decision making (SDM) is most needed when there are multiple treatment

options and no "right" choice. As with quality and experience of care, frequency of SDM may vary

by health condition. The objectives of this study were (1) to compare parent report of SDM

between a physical and a behavioral health condition and; (2) to compare parent report of SDM

between two different behavioral health conditions. Methods Data on children age 3-17 years

with asthma, attention deficit/hyperactivity disorder (ADHD), and/or autism spectrum disorder

(ASD) were drawn from the 2009/10 National Survey of Children with Special Health Care Needs.

Weighted logistic regression was used to compare a parent-reported, composite measure of SDM.

Analyses controlled for sociodemographic factors that may influence experience of SDM. Results

Compared to parents of children with asthma, parents of children with ADHD were significantly

less likely to report experiencing consistent SDM (AOR 0.73). Compared to parents of children

with ADHD, those of children with ASD had significantly lower odds of experiencing consistent

SDM (AOR 0.59). Those with both ADHD and ASD had the same odds as those with ASD alone of

experiencing consistent SDM. Conclusion Use of SDM is particularly limited in developmental and

behavioral conditions, such as ADHD and ASD. These data suggest that challenges to

implementing SDM may include disease type, complexity, and use of specialty care. Research to

identify specific barriers and facilitators of SDM is needed to inform interventions that will

promote SDM in developmental and behavioral conditions.

Liu, S., Diebo, B., Henry, J. K., Smith, J. S., Hostin, R., Cunningham, M. E., et al. (2015). The benefit

of non-operative treatment for adult spinal deformity: Identifying predictors for reaching a

minimal clinically important difference. *The Spine Journal : Official Journal of the North American

Spine Society,*

BACKGROUND CONTEXT: Adult spinal deformity (ASD) patients may gain a MCID in one or more

of the HRQOL instruments without surgical intervention. This study identifies baseline

characteristics of this subset of non-operative patients and proposes predictors of those most

likely to benefit. PURPOSE: Determine factors that affect likelihood of non-operative patients to

reach minimum clinically important difference (MCID). STUDY DESIGN/SETTING: Retrospective review of prospective, multi-center database. PATIENT SAMPLE: Non-operative ASD patients. OUTCOME MEASURES: Health-related quality of life measures (HRQOL), including the Scoliosis Research Society (SRS)-22 questionnaire. METHODS: Multicenter database of 215 non-operative patients with ASD and minimum 2-year follow-up. Using a multivariate analysis, two groups were compared to identify possible predictors: those that reached an MCID in SRS Pain or Activity (n=86) at 2 years, and those who did not reach MCID (n=129). Subgroup multivariate analysis of patients with a deficit (potential improvement) in both SRS Pain and Activity (n=84) was performed. Data collection was supported by a grant from Depuy for the International Spine Study Group Foundation. RESULTS: At baseline, the non-operative patients that reached MCID had a significantly lower SRS Pain score (3.0 vs 3.6), smaller thoracolumbar (TL) Cobb angle (29.6 degrees vs. 36.5 degrees ; 87 patients with SRS-Schwab classification Lumbar or Double), sacral slope (33.1 degrees vs. 36.4 degrees), and less lumbar lordosis (46.5 degrees vs. 52.8 degrees) (all P<0.05). SRS Pain and TL Cobb were significant predictors of reaching MCID. PI-LL was significant on univariate analysis but not by multivariate (7.5 degrees vs. 2.6 degrees ; P=0.14). In the subset of severely disabled patients, worse vertebral obliquity was a predictor for not achieving MCID (P<0.05). CONCLUSIONS: Non-operative ASD patients who achieved an MCID in SRS Activity or Pain had a lower baseline SRS Pain Score and less coronal deformity in the TL region. Greater baseline pain offers significant room for potential improvement, which may be important in identifying ASD patients who have the potential to reach an MCID non-operatively. Coronal deformities in the TL region, and associated vertebral obliquity may negatively impact improvement potential with non-operative care.

Lund, A. W., Medler, T. R., Leachman, S. A., & Coussens, L. M. (2015). Lymphatic vessels, inflammation, and immunity in skin cancer. *Cancer Discovery,*
Skin is a highly ordered immune organ that coordinates rapid responses to external insult while maintaining self-tolerance. In healthy tissue, lymphatic vessels drain fluid and coordinate local immune responses; however, environmental factors induce lymphatic vessel dysfunction, leading to lymph stasis and perturbed regional immunity. These same environmental factors drive the formation of local malignancies, which are also influenced by local inflammation. Herein, we

discuss clinical and experimental evidence supporting the tenet that lymphatic vessels participate in regulation of cutaneous inflammation and immunity, and are important contributors to malignancy and potential biomarkers and targets for immunotherapy. SIGNIFICANCE: The tumor microenvironment and tumor-associated inflammation are now appreciated not only for their role in cancer progression but also for their response to therapy. The lymphatic vasculature is a less-appreciated component of this microenvironment that coordinates local inflammation and immunity and thereby critically shapes local responses. A mechanistic understanding of the complexities of lymphatic vessel function in the unique context of skin provides a model to understand how regional immune dysfunction drives cutaneous malignancies, and as such lymphatic vessels represent a biomarker of cutaneous immunity that may provide insight into cancer prognosis and effective therapy. Cancer Discov; 6(1); 1-14. (c)2015 AACR.

Lutsep, H. L., Lynn, M. J., Cotsonis, G. A., Derdeyn, C. P., Turan, T. N., Fiorella, D., et al. (2015). Does the stenting versus aggressive medical therapy trial support stenting for subgroups with intracranial stenosis? *Stroke, 46*(11), 3282-3284.

Background and Purpose-Although the Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial showed that medical therapy alone was superior to stenting plus medical therapy for preventing recurrent strokes in patients with symptomatic intracranial stenosis, we determined whether SAMMPRIS supported the use of stenting in any subpopulations of patients with symptomatic intracranial arterial stenosis. Methods-The primary outcome, 30-day stroke and death and later strokes in the territory of the qualifying artery, was compared in those with and without baseline factors in the 2 treatment arms, percutaneous transluminal angioplasty and stenting (PTAS) plus aggressive medical therapy versus aggressive medical therapy alone. Baseline factors included sex, age, race, diabetes mellitus, hypertension, lipid disorder, smoking status, type of qualifying event, qualifying event hypoperfusion symptoms, use of antithrombotic or proton pump inhibitor at baseline, days to enrollment, old infarcts in the same territory, percent stenosis, other artery stenosis, and location of the symptomatic artery. Results-A total of 451 patients were enrolled, 227 randomized to aggressive medical therapy and 224 to PTAS. Of all variables evaluated, the observed 2-year event rates were higher with PTAS than with aggressive medical therapy in the vast majority and the

interaction with treatment was not statistically significant for any of the factors. Conclusions-The SAMMPRIS results do not provide evidence to support the use of PTAS using the Wingspan stent system compared with medical treatment in any examined subpopulation of patients with symptomatic intracranial stenosis, including those with qualifying event hypoperfusion symptoms. © 2015 American Heart Association, Inc.

Madsen, R. J., Esmonde, N. O., Ramsey, K. L., & Hansen, J. E. (2015). Axillary lymph node dissection is a risk factor for major complications after immediate breast reconstruction. *Annals of Plastic Surgery,*

BACKGROUND: Complications after immediate breast reconstruction pose a significant challenge to the reconstructive surgeon. Known risk factors include smoking, obesity, age, and adjuvant oncologic therapies. Less is known about the association between axillary lymph node dissection (ALND) and the development of postoperative complications. METHODS: We conducted a retrospective study of all patients who underwent immediate breast reconstruction after mastectomy at our institution over a 10-year period. Our outcome was an occurrence of a major complication within 90 days postoperatively. For each patient, we recorded data on demographics, smoking status, pertinent medical history, reconstruction type, adjuvant chemotherapy and radiation, tumor pathology, and whether an ALND was performed. Odds ratios (OR) were calculated to estimate the risk of a complication if an ALND was performed. RESULTS: One hundred eighty-four women, with 270 surgically treated breasts, were identified as having mastectomy with immediate reconstruction between 2002 and 2012. Mean age was 49.4 years (range, 25-84 years). There were 71 mastectomies with ALND performed, with 22 complications, and 199 mastectomies without ALND, with 20 complications (31% complication rate vs 10%, respectively; OR, 3.84; P < 0.001). When adjusted for reconstruction type, smoking history, obesity, age, presence of invasive disease, chemotherapy, and radiation therapy, the OR for complications was 3.49 (P < 0.01). The most common complication was infection in both groups. CONCLUSIONS: Mastectomy with ALND is associated with a 3-fold increase in risk of major complications in women undergoing immediate breast reconstruction, even after adjustment for known risk factors and confounders. Further studies are warranted to elucidate how ALND leads to these complications and what measures can reduce their occurrence.

Mailankody, S., & Prasad, V. (2015). Susan bates,M.D., andantonio "tito" fojo,M.D., ph.D.: Thirty years of research, discovery, service, and mentorship at the national cancer institute. *Oncologist, 20*(11), 1344-1346.

Mansoor, D., Trevino, C., Ganzini, L., & Zornow, M. (2015). Negative pressure pulmonary edema after electroconvulsive therapy. *The Journal of ECT,*

Marks, K. P., Griffen, A. K., Herrera, P., Macias, M. M., Rice, C. E., & Robinson, C. (2015). Systemwide solutions to improve early intervention for developmental-behavioral concerns. *Pediatrics, 136*(6), e1492-4.

Martindale, R. G., Warren, M., Diamond, S., & Kiraly, L. (2015). *Nutritional therapy for critically ill patients* S. Karger AG.

Nutrition therapy provided early in the critical care setting has been shown to improve outcome. Appropriate and early nutrition interventions can attenuate the hyperdynamic systemic response and depressed immune reaction to injury, serious illness and major surgery. Controversies limit the uniform application and potential benefits of nutrition, including failure to accurately predict who will 'need' nutritional intervention, lack of consensus on what the optimal enteral formulation is, overreliance on parenteral nutrition, failure to maximize the use of early enteral nutrition (EN), and how much and how best to feed the morbidly obese population. Despite challenges and inconsistencies in today's critical care setting, specialized nutrition has evolved from metabolic 'support' during critical illness to a primary therapeutic intervention designed, individualized and focused to achieve metabolic optimization and mitigation of stress-induced immune and hyperdynamic systemic responses. Nutrition should be considered early and commenced after initial resuscitation has taken place. This is most effectively accomplished with the use of protocols that aggressively promote early EN, and will result in lower mortality and a reduction in major complications. Though the complexity of the heterogeneous critically ill population will always be challenging, we are developing a better understanding of immunity, metabolic needs and catabolism associated with intensive care unit admissions. © 2015 Nestec Ltd., Vevey/S. Karger AG, Basel.

Mather, A. L., & Johnson, R. L. (2015). Event-based prediction of stream turbidity using a combined cluster analysis and classification tree approach. *Journal of Hydrology, 530*, 751-761.

Stream turbidity typically increases during streamflow events; however, similar event hydrographs can produce markedly different event turbidity behaviors because many factors influence turbidity in addition to streamflow, including antecedent moisture conditions, season, and supply of turbidity-causing materials. Modeling of sub-hourly turbidity as a function of streamflow shows that event model parameters vary on an event-by-event basis. Here we examine the extent to which stream turbidity can be predicted through the prediction of event model parameters. Using three mid-sized streams from the Mid-Atlantic region of the U.S., we show the model parameter set for each event can be predicted based on the event characteristics (e.g., hydrologic, meteorologic and antecedent moisture conditions) using a combined cluster analysis and classification tree approach. The results suggest that the ratio of beginning event discharge to peak event discharge (an estimate of the event baseflow index), as well as catchment antecedent moisture, are important factors in the prediction of event turbidity. Indicators of antecedent moisture, particularly those derived from antecedent discharge, account for the majority of the splitting nodes in the classification trees for all three streams. For this study, prediction of turbidity during streamflow events is based upon observed data (e.g., measured streamflow, precipitation and air temperature). However, the results also suggest that the methods presented here can, in future work, be used in conjunction with forecasts of streamflow, precipitation and air temperature to forecast stream turbidity. © 2015 Published by Elsevier B.V.

Mazumder, R., Lambert, W. E., Nguyen, T., Bourdette, D. N., & Cameron, M. H. (2015). Fear of falling is associated with recurrent falls in people with multiple sclerosis. *International Journal of MS Care, 17*(4), 164-170.

Background: People with multiple sclerosis (MS) fall frequently, and there are few clinically valid tools to measure the risk factors for falls. We assessed the unidimensionality of the 7-item Falls Efficacy Scale-International (FES-I), a measure of fear of falling, and determined whether the 7-item FES-I is associated with recurrent falls in people with MS. Methods: Falls were counted prospectively for 6 months using fall calendars in 58 people with MS (age, 18-50 years;

Expanded Disability Status Scale score, 0-6). The FES-I was administered at baseline, and its unidimensionality was assessed by confirmatory factor analysis. The relationship between FES-I score and future falls, after adjusting for recurrent falls in the past year, was assessed by logistic regression. Results: Fifty-four participants who completed all assessments were included in the analysis. Goodness-of-fit indices confirmed a single-factor solution for the 7-item FES-I (discrepancy χ2, P = .101; Tucker-Lewis index, 0.953; comparative fit index, 0.969; root mean square error of approximation, 0.098). There was a significant association between fear of falling and falls in the following 3 months, independent of recurrent falls in the past year (odds ratio = 1.22, 95% confidence interval, 1.04-1.43, P = .016). Conclusions: The 7-item FES-I demonstrates good construct validity, allowing the total score to be used as a measure of fear of falling in people with MS. Fear of falling, as measured by the 7-item FES-I, is associated with future recurrent falls independent of past recurrent falls in people with MS. © 2015 Consortium of Multiple Sclerosis Centers.

McAllister, M., Levett-Jones, T., Petrini, M. A., & Lasater, K. (2015). The viewing room: A lens for developing ethical comportment. *Nurse Education in Practice,*
Healthcare is dynamic and complex, and against this background, nursing students must negotiate the transition from lay person to healthcare professional. Diverse life experiences and learning styles can further complicate this journey of transformation. The contemporary role of the nurse includes caring for and making clinical decisions about patients based on ethical principles. Learning about and integrating ethical comportment as part of the transformative journey requires nurse educators to create and implement learning experiences that challenge nursing students to think deeply and broadly about the experiences they encounter, to question their previous assumptions and prejudices, to consider the world of healthcare through a new lens, and to reflect on and learn from the process. The judicious use of film has the potential to assist students to recognize and develop ethical comportment as they prepare for real-world clinical practice experiences. In this paper, we present three film exemplars and related teaching strategies designed to facilitate transformative learning and development of ethical comportment.

Means, C., Camacho, M., & Capasso, R. (2015). Long-term outcomes of radiofrequency ablation of the inferior turbinates. *Indian Journal of Otolaryngology and Head and Neck Surgery,* Radiofrequency ablation of the inferior turbinates (RFAIT) is a minimally invasive surgical technique that reduces turbinate size and decreases nasal obstruction. Few studies have assessed long-term outcomes of this procedure using standardized, symptom-specific evaluation instruments. The primary aim of this study is to assess the long-term effectiveness of RFAIT using a standardized, symptom-specific evaluation instrument. An additional outcome evaluated is the effect of RFAIT on therapeutic CPAP pressures in centimetres of water pressure (cwp) and overall CPAP use. Patients who had received RFAIT >14 months previously were identified via retrospective chart review and underwent a telephone interview with several questions to include the Nasal Obstruction Symptom Evaluation (NOSE) scale. Additionally, data regarding therapeutic pressures for continuous positive pressure devices (CPAP) and CPAP use was obtained for patients using these devices as treatment for obstructive sleep apnoea. The average NOSE scale score for the 40 patients who completed the NOSE scale questionnaire in our study was 6.35 ± 3.98 (0-20 scale). Crusting and mild, self-resolving epistaxis were the most common complications in the perioperative period. In general, unforeseen complications occurred in 14 months post-procedure. © 2015 Association of Otolaryngologists of India

Midgett, M., Chivukula, V. K., Dorn, C., Wallace, S., & Rugonyi, S. (2015). Blood flow through the embryonic heart outflow tract during cardiac looping in HH13-HH18 chicken embryos. *Journal of the Royal Society Interface, 12*(111)
Blood flow is inherently linked to embryonic cardiac development, as haemodynamic forces exerted by flow stimulate mechanotransduction mechanisms that modulate cardiac growth and remodelling. This study evaluated blood flow in the embryonic heart outflow tract (OFT) during normal development at each stage between HH13 and HH18 in chicken embryos, in order to characterize changes in haemodynamic conditions during critical cardiac looping transformations. Two-dimensional optical coherence tomography was used to simultaneously acquire both structural and Doppler flow images, in order to extract blood flow velocity and structural information and estimate haemodynamic measures. From HH13 to HH18, peak blood flow rate increased by 2.4-fold and stroke volume increased by 2.1-fold. Wall shear rate (WSR) and lumen

diameter data suggest that changes in blood flow during HH13-HH18 may induce a shear-mediated vasodilation response in the OFT. Embryo-specific four-dimensional computational fluid dynamics modelling at HH13 and HH18 complemented experimental observations and indicated heterogeneous WSR distributions over the OFT. Characterizing changes in haemodynamics during cardiac looping will help us better understand the way normal blood flow impacts proper cardiac development.

Morasco, B. J., Peters, D., Krebs, E. E., Kovas, A. E., Hart, K., & Dobscha, S. K. (2015). Predictors of urine drug testing for patients with chronic pain: Results from a national cohort of U.S. veterans. *Substance Abuse,* , 0.

BACKGROUND: Urine drug testing (UDT) is recommended for all patients who initiate chronic opioid therapy (COT) for the treatment of chronic pain; however, it is infrequently utilized. Some prior research has identified factors which may predict UDT, but studies have been limited. The purpose of this study is to examine the rate and predictors of UDT among a national sample of patients with chronic pain who had new initiations of COT. METHODS: Administrative data were examined for all veterans receiving medical care at Department of Veterans' Affairs medical facilities who had new initiations of chronic opioid therapy (COT) during fiscal year 2011. RESULTS: Nineteen percent of patients who had new initiations of COT for chronic non-cancer pain received UDT within 90 days of starting opioids. In adjusted analyses, patient-level factors that predicted increased likelihood of UDT included male gender (Risk Ratio [RR] = 1.23, 95% Confidence Interval [CI] = 1.02-1.49), black race (RR = 1.20, 95% CI = 1.06-1.37), divorced/separated marital status (RR = 1.13, 95% CI = 1.02-1.25), higher pain intensity (RR = 1.03, 95% CI = 1.01-1.05), comorbid substance use disorder (RR = 1.42, 95% CI = 1.27-1.60), PTSD (RR = 1.14, 95% CI = 1.01-1.29), bipolar disorder or schizophrenia (RR = 1.29, 95% CI = 1.08-1.53), having received UDT prior to initiating opioid therapy (RR = 1.43, 95% CI = 1.26-1.62), and a higher baseline opioid dose (RR = 1.38-1.81, 95% CIs = 1.20-1.58, 1.57-2.09). Age was also associated with UDT, in a non-linear manner. Several factors were associated with lower likelihood of UDT, including living in a highly rural setting (RR = 0.62, 95% CI = 0.29-0.99), having a VA service-connected disability (RR = 0.85-0.89, 95% CIs = 0.75-0.97, 0.79-0.99), and having a nurse practitioner or physician assistant as one's primary care clinician (RR = 0.72, 95%

CI = 0.61-0.85). CONCLUSIONS: Urine drug testing was conducted with 19% of patients who had new initiations of COT. Factors that predicted UDT were multifaceted and included patient and clinician variables. Multidimensional system-level interventions may be needed to facilitate widespread implementation of UDT.

Morry, J., Ngamcherdtrakul, W., Gu, S., Goodyear, S. M., Castro, D. J., Reda, M. M., et al. (2016). Erratum to dermal delivery of HSP47 siRNA with NOX4-modulating mesoporous silica-based nanoparticles for treating fibrosis [biomaterials, 66, (2015), 41-52] DOI:10.1016/j.biomaterials.2015.07.005. *Biomaterials, 74*, 292.

Narayanan, K., Reinier, K., Uy-Evanado, A., Teodorescu, C., Zhang, L., Chugh, H., et al. (2015). Chronic obstructive pulmonary disease and risk of sudden cardiac death. *JACC: Clinical Electrophysiology, 1*(5), 381-387.

Objectives The purpose of this study was to determine whether chronic obstructive pulmonary disease (COPD) is associated with sudden cardiac death (SCD) in the community. Background COPD is linked to cardiovascular mortality; an association with SCD has not been systematically investigated in the general population. Methods In the Oregon Sudden Unexpected Death Study (approximately 1 million population), adult SCD case subjects were compared with geographic control subjects with coronary artery disease. Detailed clinical and electrocardiographic risk marker information was obtained from medical records. The association of COPD with SCD in the overall population and in a propensity score-matched dataset was assessed with logistic models. Results SCD case subjects (n = 728; age 69.9 ± 13.7 years) were more likely than control subjects (n = 548; age 67.2 ± 11.3 years) to have left ventricular ejection fraction ≤&35% (27.5% vs. 12.0%; $p < 0.0001$), COPD (30.8% vs. 12.8%, $p < 0.0001$), diabetes mellitus (47.7% vs. 31.8%; $p < 0.0001$), use short-acting beta-2 agonist agents (SBAs) (22.3% vs. 12.6%; $p < 0.0001$), and less likely to use beta-blockers (60.6% vs. 66.4%; $p = 0.03$). In multivariable analysis, COPD was significantly associated with SCD (odds ratio [OR]: 2.2; 95% confidence interval [CI]: 1.4 to 3.5; $p < 0.001$). There was no significant interaction between COPD and medications, but an interaction was identified between SBAs and beta-blockers ($p = 0.04$); SBAs were strongly associated with SCD in subjects not taking beta-blockers (OR: 3.3;

95% CI: 1.4 to 7.7; p = 0.005) but not in those taking beta-blockers (OR: 1.3; 95% CI: 0.7 to 2.3; p = 0.39). The COPD-SCD association was maintained in a propensity score-matched analysis. Conclusions COPD is associated with SCD risk in the community independent of medications, electrocardiographic risk markers, and left ventricular ejection fraction. Among other mechanisms, pro-arrhythmogenic right ventricular remodeling and systemic inflammation warrant further investigation. © 2015 American College of Cardiology Foundation.

Nilsagard, Y., Gunn, H., Freeman, J., Hoang, P., Lord, S., Mazumder, R., et al. (2015). Falls in people with MS--an individual data meta-analysis from studies from australia, sweden, united kingdom and the united states. *Multiple Sclerosis (Houndmills, Basingstoke, England), 21*(1), 92-100. BACKGROUND: Falls are common in people with multiple sclerosis (PwMS). Previous studies have generally included small samples and had varied methods. OBJECTIVES: The objectives of this paper are to compile fall rates across a broad range of ages and disease severity and to definitively assess the extent to which MS-associated and demographic factors influence fall rates. METHODS: Individual data from studies in four countries that prospectively measured falls for three months were analyzed. We determined fall rates, prevalence of fallers (>/=1 falls) and frequent fallers (>/=2 falls), location and timing of falls, and fall-related demographic factors. RESULTS: A total of 537 participants reported 1721 falls: 56% were fallers and 37% frequent fallers. Most falls occurred indoors (65%) between 6 a.m. and 6 p.m. (75%). Primary progressive MS was associated with significantly increased odds of being a faller (odds ratio (OR) 2.02; CI 1.08-3.78). Fall risk peaked at EDSS levels of 4.0 and 6.0 with significant ORs between 5.30 (2.23-12.64) and 5.10 (2.08-12.47). The fall rate was lower in women than men (relative risk (RR) 0.80; CI 0.67-0.94) and decreased with increasing age (RR 0.97 for each year, CI 0.95-0.98). CONCLUSION: PwMS are at high risk of falls and there are important associations between falls and MS-associated disability, gender and age.

Nzabarushimana, E., Prior, S., Miousse, I. R., Pathak, R., Allen, A. R., Latendresse, J., et al. (2015). Combined exposure to protons and (56)fe leads to overexpression of Il13 and reactivation of repetitive elements in the mouse lung. *Life Sciences in Space Research, 7*, 1-8. Interest in deep space exploration underlines the needs to investigate the effects of exposure to

combined sources of space radiation. The lung is a target organ for radiation, and exposure to protons and heavy ions as radiation sources may lead to the development of degenerative disease and cancer. In this study, we evaluated the pro-fibrotic and epigenetic effects of exposure to protons (150 MeV/nucleon, 0.1 Gy) and heavy iron ions ((56)Fe, 600 MeV/nucleon, 0.5 Gy) alone or in combination (protons on Day 1 and (56)Fe on Day 2) in C57BL/6 male mice 4 weeks after irradiation. Exposure to (56)Fe, proton or in combination, did not result in histopathological changes in the murine lung. At the same time, combined exposure to protons and (56)Fe resulted in pronounced molecular alterations in comparison with either source of radiation alone. Specifically, we observed a substantial increase in the expression of cytokine Il13, loss of expression of DNA methyltransferase Dnmt1, and reactivation of LINE-1, SINE B1 retrotransposons, and major and minor satellites. Given the deleterious potential of the observed effects that may lead to development of chronic lung injury, pulmonary fibrosis, and cancer, future studies devoted to the investigation of the long-term effects of combined exposures to proton and heavy ions are clearly needed.

Obaseki, D. O., Erhabor, G. E., Gnatiuc, L., Adewole, O. O., Buist, S. A., & Burney, P. G. (2015). Chronic airflow obstruction in a black african population: Results of BOLD study, ile-ife, nigeria. *COPD: Journal of Chronic Obstructive Pulmonary Disease,*

Global estimates suggest that Chronic Obstructive Pulmonary Disease (COPD) is emerging as a leading cause of death in developing countries but there are few spirometry-based general population data on its prevalence and risk factors in sub-Saharan Africa. We used the Burden of Obstructive Lung Disease (BOLD) protocol to select a representative sample of adults aged 40 years and above in Ile-Ife, Nigeria. All the participants underwent spirometry and provided information on smoking history, biomass and occupational exposures as well as diagnosed respiratory diseases and symptoms. Chronic Airflow Obstruction (CAO) was defined as the ratio of post-bronchodilator (BD) one second Forced Expiratory Volume (FEV1) to Forced Vital Capacity (FVC) below the lower limit of normal (LLN) of the population distribution for FEV1/FVC. The overall prevalence of obstruction (post-BD FEV1/FVC < LLN) was 7.7% (2.7% above LLN) using Global Lung Function Initiative (GLI) equations. It was associated with few respiratory symptoms; 0.3% reported a previous doctor-diagnosed chronic bronchitis, emphysema or COPD.

Independent predictors included a lack of education (OR 2·5, 95% CI: 1.0, 6.4) and a diagnosis of either TB (OR 23.4, 95% CI: 2.0, 278.6) or asthma (OR 35.4, 95%CI: 4.9, 255.8). There was no association with the use of firewood or coal for cooking or heating. The vast majority of this population (89%) are never smokers. We conclude that the prevalence of CAO is low in Ile-Ife, Nigeria and unrelated to biomass exposure. The key independent predictors are poor education, and previous diagnosis of tuberculosis or asthma. Copyright © 2015 Taylor & Francis

Onega, T., Reisch, L. M., Frederick, P. D., Geller, B. M., Nelson, H. D., Lott, J. P., et al. (2015). Use of digital whole slide imaging in dermatopathology. *Journal of Digital Imaging,*
Digital whole slide imaging (WSI) is an emerging technology for pathology interpretation, with specific challenges for dermatopathology, yet little is known about pathologists' practice patterns or perceptions regarding WSI for interpretation of melanocytic lesions. A national sample of pathologists (N = 207) was recruited from 864 invited pathologists from ten US states (CA, CT, HI, IA, KY, LA, NJ, NM, UT, and WA). Pathologists who had interpreted melanocytic lesions in the past year were surveyed in this cross-sectional study. The survey included questions on pathologists' experience, WSI practice patterns and perceptions using a 6-point Likert scale. Agreement was summarized with descriptive statistics to characterize pathologists' use and perceptions of WSI. The majority of participating pathologists were between 40 and 59 years of age (62 %) and not affiliated with an academic medical center (71 %). Use of WSI was seen more often among dermatopathologists and participants affiliated with an academic medical center. Experience with WSI was reported by 41 %, with the most common type of use being for education and testing (CME, board exams, and teaching in general, 71 %), and clinical use at tumor boards and conferences (44 %). Most respondents (77 %) agreed that accurate diagnoses can be made with this technology, and 59 % agreed that benefits of WSI outweigh concerns. However, 78 % of pathologists reported that digital slides are too slow for routine clinical interpretation. The respondents were equally split as to whether they would like to adopt WSI (49 %) or not (51 %). The majority of pathologists who interpret melanocytic lesions do not use WSI, but among pathologists who do, use is largely for CME, licensure/board exams, and teaching. Positive perceptions regarding WSI slightly outweigh negative perceptions. Understanding

practice patterns with WSI as dissemination advances may facilitate concordance of perceptions with adoption of the technology.

Orb, Q., Mace, J. C., DeConde, A. S., Steele, T. O., Cox, S. T., Smith, T. L., et al. (2015). Patients electing medical vs surgical treatment: Emotional domain of the rhinosinusitis disability index associates with treatment selection. *International Forum of Allergy & Rhinology,*
BACKGROUND: The Rhinosinusitis Disability Index (RSDI) consists of multiple subdomains shown to be useful in studying chronic rhinosinusitis (CRS). The objective of this study was to determine if RSDI subdomain scores are associated with selection of treatment modality (endoscopic sinus surgery [ESS] or continued medical management [CMM]) in subjects with CRS. METHODS: Patients with CRS were prospectively enrolled into a multi-institutional cohort study. Following an initial period of medical management, patients elected to undergo treatment with either ESS or CMM. Baseline RSDI total and subdomain scores were compared between patients electing different treatment modalities. RESULTS: A total of 684 subjects were enrolled with 122 (17.8%) electing CMM and 562 (82.2%) electing ESS. When compared to patients undergoing CMM, patients electing ESS exhibited significantly higher mean baseline RSDI total scores (mean +/- standard deviation [SD]: 48.1 +/- 24.9 vs 40.1 +/- 24.1; p = 0.001) and subdomain scores (emotional: 13.2 +/- 9.1 vs 10.4 +/- 8.3; p = 0.001; functional: 15.3 +/- 8.9 vs 12.6 +/- 8.4; p = 0.002; and physical: 19.6 +/- 9.3 vs 17.1 +/- 9.6; p = 0.007). Emotional subdomain scores were found to be the most associated with choice of treatment modality. CONCLUSION: Patients with CRS electing ESS had worse baseline RSDI total and subdomain scores compared to those electing CMM. Although both rhinologic and nonrhinologic symptoms contributed to the selection of treatment modality, emotional symptoms appeared to exhibit the greatest influence on patient-centered treatment decisions.

Parish, M., Rohlman, D. S., Elliot, D. L., & Lasarev, M. (2015). Factors associated with occupational injuries in seasonal young workers. *Occupational Medicine (Oxford, England),*
BACKGROUND: Younger workers are more likely to be injured on the job than older workers. Investigation tends to focus on work-related explanatory factors but often neglects non-work-related causes. AIMS: To identify both work- and non-work-related factors that contribute to

younger workers' injuries in seasonal work. METHODS: Two surveys of a set of seasonal parks and recreation workers were conducted measuring health and safety behaviours and self-reported injuries. RESULTS: Seventy per cent reported an injury at work over the summer. Among young workers, each additional year of age was associated with an almost 50% increase in injury rate ($P < 0.05$). Odds of injury in women were three times those for men ($P < 0.05$). We observed a linear relationship between average hours worked per week and injuries ($P < 0.001$). Alcohol abuse ($P < 0.05$) was also associated with injuries. CONCLUSIONS: Higher injury rates among younger workers in this sample is multifactorial and encompasses both work and non-work factors and suggest that more global approaches are required to address young worker safety.

Prasad, V., & Vandross, A. (2015). Characteristics of exceptional or super responders to cancer drugs. *Mayo Clinic Proceedings,*

OBJECTIVE: To summarize case reports of exceptional and super responders already published in the biomedical literature. PATIENTS AND METHODS: We searched for published case reports or abstracts of exceptional or super responders to a cancer drug using PubMed and Google Scholar search engines. Pooling such reports is widely considered a promising research strategy and the subject of several ongoing investigations, including the National Cancer Institute's Exceptional Responders Initiative. All articles were read in full, including relevant references. We extracted clinical characteristics of exceptional or super responders, including age, tumor type, drug, genetic mutations, depth of response, duration of response, number of previous lines of therapy, duration of response to a previous line of therapy, and the number of patients treated similarly to identify the exceptional case. This study was performed between March 1, 2015, and April 30, 2015. RESULTS: Among 489 articles, 32 exceptional responders were identified. The most common malignancies described were renal cell cancer (5 of 32 [16%]) and urothelial carcinoma (4 of 32 [13%]). The use of targeted agents was common in these cases (26 of 32 [81%]), particularly inhibitors of the mTOR pathway (16 of 32 [50%]). The median duration of response among responders was 17.5 months, and 59% (19 of 32) of the patients were last known to be alive with continuing response or stable disease. Notably, 46% (12 of 26) of the patients had received 2 or more previous lines of therapy and 6 of the 32 cases (19%) did not report this

information. Few authors report the number of patients treated similarly to observe the super response (12 of 32 [38%]). CONCLUSION: Exceptional or super responders to cancer drugs have been described in the literature; however, there is incompleteness in the reporting of relevant data that may help clarify whether such responses are secondary to treatment or reflect underlying biology.

Pulido, J. S., Flaxel, C. J., Adelman, R. A., Hyman, L., Folk, J. C., & Olsen, T. W. (2015). Retinal vein occlusions preferred practice pattern guidelines. *Ophthalmology,*

Quanjer, P. H., Ruppel, G., Brusasco, V., Perez-Padilla, R., Fragoso, C. A., Culver, B. H., et al. (2015). COPD (confusion over proper diagnosis) in the zone of maximum uncertainty. *The European Respiratory Journal, 46*(5), 1523-1524.

Raber, J., Marzulla, T., Kronenberg, A., & Turker, M. S. (2015). (16)oxygen irradiation enhances cued fear memory in B6D2F1 mice. *Life Sciences in Space Research, 7*, 61-65.
The space radiation environment includes energetic charged particles that may impact cognitive performance. We assessed the effects of (16)O ion irradiation on cognitive performance of C57BL/6J x DBA/2J F1 (B6D2F1) mice at OHSU (Portland, OR) one month following irradiation at Brookhaven National Laboratory (BNL, Upton, NY). Hippocampus-dependent contextual fear memory and hippocampus-independent cued fear memory of B6D2F1 mice were tested. (16)O ion exposure enhanced cued fear memory. This effect showed a bell-shaped dose response curve. Cued fear memory was significantly stronger in mice irradiated with (16)O ions at a dose of 0.4 or 0.8 Gy than in sham-irradiated mice or following irradiation at 1.6 Gy. In contrast to cued fear memory, contextual fear memory was not affected following (16)O ion irradiation at the doses used in this study. These data indicate that the amygdala might be particularly susceptible to effects of (16)O ion exposure.

Rajhbeharrysingh, U., El Youssef, J., Leon, E., Lasarev, M. R., Klein, R., Vanek, C., et al. (2015). Expanding the net: The re-evaluation of the multidimensional nomogram calculating the upper limit of normal PTH (maxPTH) in the setting of secondary hyperparathyroidism and the development of the MultIdimensional predictive hyperparaTHyroid model (mi-PTH). *Surgery,*

BACKGROUND: The multidimensional nomogram calculating the upper limit of normal PTH (maxPTH) model identifies a personalized upper limit of normal parathyroid hormone (PTH) and successfully predicts classical primary hyperparathyroidism (PHP). We aimed to assess whether maxPTH can distinguish normocalcemic PHP (NCPHP) from secondary hyperparathyroidism (SHP), including subjects who underwent bariatric surgery (BrS). METHODS: A total of 172 subjects with 359 complete datasets of serum calcium (Ca), 25-OH vitamin D, and intact PTH from Oregon were analyzed: 123 subjects (212 datasets) with PHP and 47 (143) with SHP, including 28 (100) with previous BrS. An improved prediction model, MultIdimensional evaluation for Primary hyperparaTHyroidism (Mi-PTH), was created with the same variables as maxPTH by the use of a combined cohort (995 subjects) including participants from previous studies. RESULTS: In the Oregon cohort, maxPTH's sensitivity was 100% for classical PHP and 89% for NCPHP, but only 50% for normohormonal PHP (NHPHP) and 40% specific for SHP. In comparison, although sensitivity for NCPHP was similar (89%), Mi-PTH vastly improved SHP specificity (85%). In the combined cohort, Mi-PTH had better sensitivity of 98.5% (vs 95%) and specificity 97% (vs 85%). CONCLUSION: MaxPTH was sensitive in detecting PHP; however, there was low specificity for SHP, especially in patients who underwent BrS. The creation of Mi-PTH provided improved performance measures but requires further prospective evaluation.

Reisch, L. M., Carney, P. A., Oster, N. V., Weaver, D. L., Nelson, H. D., Frederick, P. D., et al. (2015). Medical malpractice concerns and defensive medicine: A nationwide survey of breast pathologists. *American Journal of Clinical Pathology, 144*(6), 916-922.

OBJECTIVES: "Assurance behaviors" in medical practice involve providing additional services of marginal or no medical value to avoid adverse outcomes, deter patients from filing malpractice claims, or ensure that legal standards of care were met. The extent to which concerns about medical malpractice influence assurance behaviors of pathologists interpreting breast specimens is unknown. METHODS: Breast pathologists (n = 252) enrolled in a nationwide study completed an online survey of attitudes regarding malpractice and perceived alterations in interpretive behavior due to concerns of malpractice. Associations between pathologist characteristics and the impact of malpractice concerns on personal and colleagues' assurance behaviors were determined by chi(2) and logistic regression analysis. RESULTS: Most participants reported using one or more

assurance behaviors due to concerns about medical malpractice for both their personal (88%) and colleagues' (88%) practices, including ordering additional stains, recommending additional surgical sampling, obtaining second reviews, or choosing the more severe diagnosis for borderline cases. Nervousness over breast pathology was positively associated with assurance behavior and remained statistically significant in a multivariable logistic regression model (odds ratio, 2.5; 95% confidence interval, 1.0-6.1; P = .043). CONCLUSIONS: Practicing US breast pathologists report exercising defensive medicine by using assurance behaviors due to malpractice concerns.

Rich, P., Gooderham, M., Bachelez, H., Goncalves, J., Day, R. M., Chen, R., et al. (2015). Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with difficult-to-treat nail and scalp psoriasis: Results of 2 phase III randomized, controlled trials (ESTEEM 1 and ESTEEM 2). *Journal of the American Academy of Dermatology,*

BACKGROUND: In the phase III double-blind Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) 1 and 2, apremilast, an oral phosphodiesterase 4 inhibitor, demonstrated efficacy in moderate to severe psoriasis. OBJECTIVE: We sought to evaluate efficacy of apremilast in nail/scalp psoriasis in ESTEEM 1 and 2. METHODS: A total of 1255 patients were randomized (2:1) to apremilast 30 mg twice daily or placebo. At week 16, placebo patients switched to apremilast through week 32, followed by a randomized withdrawal phase to week 52. A priori efficacy analyses included patients with nail (target nail Nail Psoriasis Severity Index score >/=1) and moderate to very severe scalp (Scalp Physician Global Assessment score >/=3) psoriasis at baseline. RESULTS: At baseline, 66.1% and 64.7% of patients had nail psoriasis; 66.7% and 65.5% had moderate to very severe scalp psoriasis in ESTEEM 1 and 2. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index score versus placebo; mean percent change: -22.5% versus +6.5% (ESTEEM 1; P < .0001) and -29.0% versus -7.1% (ESTEEM 2; P = .0052). At week 16, apremilast produced greater NAPSI-50 response (50% reduction from baseline in target nail Nail Psoriasis Severity Index score) versus placebo (both studies P < .0001) and ScPGA response (Scalp Physician Global Assessment score 0 or 1) versus placebo (both studies P < .0001). Improvements were generally maintained over 52 weeks in patients with Psoriasis Area and Severity Index response at week 32. LIMITATIONS:

Baseline randomization was not stratified for nail/scalp psoriasis. CONCLUSION: Apremilast reduces the severity of nail/scalp psoriasis.

Riches, M. L., Trifilio, S., Chen, M., Ahn, K. W., Langston, A., Lazarus, H. M., et al. (2015). Risk factors and impact of non-aspergillus mold infections following allogeneic HCT: A CIBMTR infection and immune reconstitution analysis. *Bone Marrow Transplantation,*
Risk factors for non-Aspergillus mold infection (NAMI) and the impact on transplant outcome are poorly assessed in the current era of antifungal agents. Outcomes of 124 patients receiving allogeneic hematopoietic cell transplantation (HCT) diagnosed with either mucormycosis (n=72) or fusariosis (n=52) between days 0 and 365 after HCT are described and compared with a control cohort (n=11 856). Patients with NAMI had more advanced disease (mucormycois: 25%, fusariosis: 23% and controls: 18%; P=0.004) and were more likely to have a Karnofsky performance status (KPS) <90% at HCT (mucormycosis: 42%, fusariosis: 38% and controls: 28%; P=0.048). The 1-year survival after HCT was 22% (15-29%) for cases and was significantly inferior compared with controls (65% (64-65%); P<0.001). Survival from infection was similarly dismal regardless of mucormycosis: 15% (8-25%) and fusariosis: 21% (11-33%). In multivariable analysis, NAMI was associated with a sixfold higher risk of death (P<0.0001) regardless of the site or timing of infection. Risk factors for mucormycosis include preceding acute GvHD, prior Aspergillus infection and older age. For fusariosis, increased risks including receipt of cord blood, prior CMV infection and transplant before May 2002. In conclusion, NAMI occurs infrequently, is associated with high mortality and appears with similar frequency in the current antifungal era.Bone Marrow Transplantation advance online publication, 2 November 2015; doi:10.1038/bmt.2015.263.

Rivera, H. M., Kievit, P., Kirigiti, M. A., Bauman, L. A., Baquero, K., Blundell, P., et al. (2015). Maternal high-fat diet and obesity impact palatable food intake and dopamine signaling in nonhuman primate offspring. *Obesity (Silver Spring, Md.), 23*(11), 2157-2164.
OBJECTIVE: To utilize a nonhuman primate model to examine the impact of maternal high-fat diet (HFD) consumption and pre-pregnancy obesity on offspring intake of palatable food and to examine whether maternal HFD consumption impaired development of the dopamine system,

critical for the regulation of hedonic feeding. METHODS: The impact of exposure to maternal HFD and obesity on offspring consumption of diets of varying composition was assessed after weaning. The influence of maternal HFD consumption on the development of the prefrontal cortex-dopaminergic system at 13 months of age was also examined. RESULTS: During a preference test, offspring exposed to maternal HFD consumption and obesity displayed increased intake of food high in fat and sugar content relative to offspring from lean control mothers. Maternal HFD consumption suppressed offspring dopamine signaling (as assessed by immunohistochemistry) relative to control offspring. Specifically, there was decreased abundance of dopamine fibers and of dopamine receptor 1 and 2 proteins. CONCLUSIONS: This study reveals that offspring exposed to both maternal HFD consumption and maternal obesity during early development are at increased risk for obesity due to overconsumption of palatable energy-dense food, a behavior that may be related to reduced central dopamine signaling.

Rubiano, A. M., Carney, N., Chesnut, R., & Puyana, J. C. (2015). Global neurotrauma research challenges and opportunities. *Nature, 527*(7578), S193-7.

Traumatic injury to the brain or spinal cord is one of the most serious public health problems worldwide. The devastating impact of 'trauma', a term used to define the global burden of disease related to all injuries, is the leading cause of loss of human potential across the globe, especially in low- and middle-income countries. Enormous challenges must be met to significantly advance neurotrauma research around the world, specifically in underserved and austere environments. Neurotrauma research at the global level needs to be contextualized: different regions have their own needs and obstacles. Interventions that are not considered a priority in some regions could be a priority for others. The introduction of inexpensive and innovative interventions, including mobile technologies and e-health applications, focused on policy management improvement are essential and should be applicable to the needs of the local environment. The simple transfer of a clinical question from resource-rich environments to those of low- and middle-income countries that lack sophisticated interventions may not be the best strategy to address these countries' needs. Emphasis on promoting the design of true 'ecological' studies that include the evaluation of human factors in relation to the process of care, analytical

descriptions of health systems, and how leadership is best applied in medical communities and society as a whole will become crucial.

Sachdev, P. S., Lipnicki, D. M., Kochan, N. A., Crawford, J. D., Thalamuthu, A., Andrews, G., et al. (2015). The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: The COSMIC collaboration. *PloS One, 10*(11), e0142388.

BACKGROUND: Changes in criteria and differences in populations studied and methodology have produced a wide range of prevalence estimates for mild cognitive impairment (MCI). METHODS: Uniform criteria were applied to harmonized data from 11 studies from USA, Europe, Asia and Australia, and MCI prevalence estimates determined using three separate definitions of cognitive impairment. RESULTS: The published range of MCI prevalence estimates was 5.0%-36.7%. This was reduced with all cognitive impairment definitions: performance in the bottom 6.681% (3.2%-10.8%); Clinical Dementia Rating of 0.5 (1.8%-14.9%); Mini-Mental State Examination score of 24-27 (2.1%-20.7%). Prevalences using the first definition were 5.9% overall, and increased with age (P < .001) but were unaffected by sex or the main races/ethnicities investigated (Whites and Chinese). Not completing high school increased the likelihood of MCI (P </= .01). CONCLUSION: Applying uniform criteria to harmonized data greatly reduced the variation in MCI prevalence internationally.

Sandhu, R. K., Adams, T., Sibley, C., Suhler, E. B., & Kim, D. H. (2015). Granulomatosis with polyangiitis (gpa) presenting with frosted branch angiitis. *Retinal Cases & Brief Reports,*

PURPOSE: To report a case of frosted branch angiitis in a patient with granulomatosis with polyangiitis. METHODS: Clinical case report. Imaging was obtained with pseudo-color scanning laser ophthalmoscope photographs, fluorescein angiography, spectral domain optical coherence tomography, and B-scan ultrasound. RESULTS: A 24-year-old woman with a clinical history of granulomatosis with polyangiitis who presented with acute vision loss was found to have frosted branch angiitis with concurrent posterior scleritis and orbital inflammation. These findings improved rapidly after initiation of high-dose intravenous solumedrol. CONCLUSION: This is a unique case of frosted branch angiitis associated with granulomatosis with polyangiitis. The authors are not aware of a previous report of this association. Although rare, retinal vasculitis

should be recognized as a potential complication of granulomatosis with polyangiitis and can respond rapidly to prompt initiation of therapy.

Saultz, J. (2015). Family medicine student interest. *Family Medicine, 47*(10), 761-762.

Saultz, J. (2015). Integrating behavioral health and primary care. *Family Medicine, 47*(7), 509-510.

Scariati, P., Nelson, L., Watson, L., Bedrick, S., & Eden, K. B. (2015). Impact of a decision aid on reducing uncertainty: Pilot study of women in their 40s and screening mammography. *BMC Medical Informatics and Decision Making, 15*(1), 89-015-0210-2.
BACKGROUND: In 2009 the United States Preventive Services Task Force updated its breast cancer screening guidelines to recommend that average-risk women obtain a screening mammogram every two years starting at age 50 instead of annually starting at age 40. Inconsistencies in data regarding the benefit versus risk of routine screening for women less than 50-years-of-age led to a second recommendation - that women in their forties engage in a shared decision making process with their provider to make an individualized choice about screening mammography that was right for them. In response, a web-based interactive mammography screening decision aid was developed and evaluated. METHODS: The decision aid was developed using an agile, iterative process. It was further honed based on feedback from clinical and technical subject matter experts. A convenience sample of 51 age- and risk-appropriate women was recruited to pilot the aid. Pre-post decisional conflict and screening choice was assessed. RESULTS: Women reported a significant reduction in overall decisional conflict after using the decision aid (Z = -5.3, p < 0.001). These participants also reported statistically significant reductions in each of the decisional conflict subscales: feeling uncertain (Z = -4.7, p < 0.001), feeling uninformed (Z = -5.2, p < 0.001), feeling unclear about values (Z = -5.0, p < 0.001), and feeling unsupported (Z = -4.0, p < 0.001). However, a woman's intention to obtain a screening mammogram in the next 1-2 years was not significantly changed (Wilcoxon signed-rank Z = -1.508, p = 0.132). CONCLUSION: This mammography screening decision aid brings value to patient care not by impacting what a woman chooses but by lending clarity to why or how she chooses it.

Schallhorn, J. M., Holiman, J. D., Stoeger, C. G., & Chamberlain, W. (2015). Quantification and patterns of endothelial cell loss due to eye bank preparation and injector method in descemet membrane endothelial keratoplasty tissues. *Cornea,*

PURPOSE: To evaluate endothelial cell damage after eye bank preparation and passage through 1 of 2 different injectors for Descemet membrane endothelial keratoplasty grafts. METHODS: Eighteen Descemet membrane endothelial keratoplasty grafts were prepared by Lions VisionGift with the standard partial prepeel technique and placement of an S-stamp for orientation. The grafts were randomly assigned to injection with either a glass-modified Jones tube injector (Gunther Weiss Scientific Glass) or a closed-system intraocular lens injector (Viscoject 2.2; Medicel). After injection, the grafts were stained with the vital fluorescent dye Calcein AM and digitally imaged. The percentage of cell loss was calculated by measuring the area of nonfluorescent pixels and dividing it by the total graft area pixels. RESULTS: Grafts injected using the modified Jones tube injector had an overall cell loss of 27% +/- 5% [95% confidence interval, 21%-35%]. Grafts injected using the closed-system intraocular lens injector had a cell loss of 32% +/- 8% (95% confidence interval, 21%-45%). This difference was not statistically significant (P = 0.3). Several damage patterns including damage due to S-stamp placement were observed, but they did not correlate with injector type. CONCLUSIONS: In this in vitro study, there was no difference in the cell loss associated with the injector method. Grafts in both groups sustained significant cell loss and displayed evidence of graft preparation and S-stamp placement. Improvement in graft preparation and injection methods may improve cell retention.

Schoner, A., Tyrrell, C., Wu, M., Gelow, J. M., Hayes, A. A., Lindner, J. R., et al. (2015). Endocardial endothelial dysfunction progressively disrupts initially anti then pro-thrombotic pathways in heart failure mice. *PloS One, 10*(11), e0142940.

OBJECTIVE: An experimental model of endocardial thrombosis has not been developed and endocardial endothelial dysfunction in heart failure (HF) is understudied. We sought to determine whether disruption of the endothelial anti-coagulant activated protein C (APC) pathway in CREBA133 HF mice promotes endocardial thrombosis in the acute decompensated phase of the disease, and whether alterations in von Willebrand factor (vWF) secretion from HF endocardium reduces thrombus formation as HF stabilizes. APPROACH AND RESULTS: Echocardiography was

used to follow HF development and to detect endocardial thrombi in CREBA133 mice. Endocardial thrombi incidence was confirmed with immunohistochemistry and histology. In early and acute decompensated phases of HF, CREBA133 mice had the highest incidence of endocardial thrombi and these mice also had a shorter tail-bleeding index consistent with a pro-thrombotic milieu. Both APC generation, and expression of receptors that promote APC function (thrombomodulin, endothelial protein C receptor, protein S), were suppressed in the endocardium of acute decompensated HF mice. However, in stable compensated HF mice, an attenuation occurred for vWF protein content and secretion from endocardial endothelial cells, vWF-dependent platelet agglutination (by ristocetin), and thrombin generation on the endocardial surface.

CONCLUSIONS: CREBA133 mice develop HF and endocardial endothelial dysfunction. Attenuation of the anti-coagulant APC pathway promotes endocardial thrombosis in early and acute decompensated phases of HF. However, in stable compensated HF mice, disruptions in endothelial vWF expression and extrusion may actually reduce the incidence of endocardial thrombosis.

Selph, S., Blazina, I., & Chou, R. (2015). In response. *Annals of Internal Medicine, 163*(9), 726-727.

Seo, J. W., Jones, S. M., Hostetter, T. A., Iliff, J. J., & West, G. A. (2015). Methamphetamine induces the release of endothelin. *Journal of Neuroscience Research,*
Methamphetamine is a potent psychostimulant drug of abuse that increases release and blocks reuptake of dopamine, producing intense euphoria, factors that may contribute to its widespread abuse. It also produces severe neurotoxicity resulting from oxidative stress, DNA damage, blood-brain barrier disruption, microgliosis, and mitochondrial dysfunction. Intracerebral hemorrhagic and ischemic stroke have been reported after intravenous and oral abuse of methamphetamine. Several studies have shown that methamphetamine causes vasoconstriction of vessels. This study investigates the effect of methamphetamine on endothelin-1 (ET-1) release in mouse brain endothelial cells by ELISA. ET-1 transcription as well as endothelial nitric oxide synthase (eNOS) activation and transcription were measured following methamphetamine treatment. We also examine the effect of methamphetamine on isolated cerebral arteriolar vessels from C57BL/6 mice. Penetrating middle cerebral arterioles were cannulated at both ends with a micropipette

system. Methamphetamine was applied extraluminally, and the vascular response was investigated. Methamphetamine treatment of mouse brain endothelial cells resulted in ET-1 release and a transient increase in ET-1 message. The activity and transcription of eNOS were only slightly enhanced after 24 hr of treatment with methamphetamine. In addition, methamphetamine caused significant vasoconstriction of isolated mouse intracerebral arterioles. The vasoconstrictive effect of methamphetamine was attenuated by coapplication of the endothelin receptor antagonist PD145065. These findings suggest that vasoconstriction induced by methamphetamine is mediated through the endothelin receptor and may involve an endothelin-dependent pathway. (c) 2015 Wiley Periodicals, Inc.

Sharifi, H., Masjedi, M. R., Emami, H., Ghanei, M., Eslaminejad, A., Radmand, G., et al. (2015). Burden of obstructive lung disease study in tehran: Prevalence and risk factors of chronic obstructive pulmonary disease. *Lung India, 32*(6), 572-577.

Background: Chronic obstructive pulmonary disease (COPD) was ranked the sixth-most common cause of death worldwide in 1990, but now it is the third-most common cause. The goal of the present study was to assess the prevalence and determine the causes and risk factors of COPD in Tehran. Materials and Methods: This study followed a stratified cluster sampling strategy with proportional allocation within strata. The target population was all non-institutionalized inhabitants, aged 18 to 40 in one group and over 40 in another who resided in Tehran in 2013. The core questionnaire was developed from pre-existing validated questionnaires that had already been used in multi-national studies. The single most important outcome measure obtained as part of this protocol was spirometry before and after the administration of 200 mg (two puffs) of salbutamol. Results: The most commonly reported respiratory symptoms were: sputum production in 291 patients (16.2%) [95% confidence interval (CI): 14.5-17.9%], chronic cough in 171 (9.5%) (95% CI: 8.2-10.9%), wheezing in 377 (21.0%) (95%CI: 19.1-22.9%) and dyspnea in 388 patients (21.6%) (95% CI: 19.7-23.5%). The overall COPD prevalence defined by the post-bronchodilator spirometric functional criteria was 9.2%. This value in men (10.1%) was higher than in women (8.5%); the prevalence was significantly higher in subjects aged over 55 years (P ≤ 0.002). The prevalence of COPD was strongly dependent on smoking status, especially in ex-smokers, and increased considerably with age. 69% of patients with COPD were

non-smoker. Conclusion: The high prevalence of verified COPD, a great deal of which was undiagnosed before by a physician, highlights the necessity of raising awareness of this disease among health professionals, and use of spirometry in the primary care setting. A future cross-sectional and prospective cohort study should be performed to explore all risk factors and their impact on decline in lung function and worsening of respiratory symptoms especially in non-smokers.

Sharma, A., Law, A. D., Bambery, P., Sagar, V., Wanchu, A., Dhir, V., et al. (2014). Relapsing polychondritis: Clinical presentations, disease activity and outcomes. *Orphanet Journal of Rare Diseases, 9*, 198-014-0198-1.

BACKGROUND: Relapsing polychondritis is a rare disease characterised by inflammation of cartilaginous and proteoglycan rich structures. As there are only a few published single centre case series from all across the world, we describe our experience with 26 patients at a tertiary centre in north India. METHODS: A retrospective study with all patients meeting Damiani and Levine's modification of McAdam's diagnostic criteria. Clinical details, investigations, disease activity assessment [(Relapsing Polychondritis Disease Activity Index (RPDAI)], treatment and outcomes were recorded. RESULTS: Ten men and sixteen women (median age 45 years) met the diagnostic criteria. Auricular chondritis (96%), arthritis (54%), hearing impairment (42%), ocular (42%), dermal (26%), cardiovascular (11%) and laryngotracheal involvement (11%) characterized the clinical presentations. The median RPDAI was 31 (range 9-66). Two patients died during observation. Overall survival was 92.3% (median survival 13.5 years). CONCLUSIONS: Apart from reduced laryngotracheal involvement, RP in India was clinically similar to recorded patterns elsewhere.

Sinclair, L., Griglock, T. M., Mench, A., Lamoureux, R., Cormack, B., Bidari, S., et al. (2015). Determining organ doses from CT with direct measurements in postmortem subjects: Part 2-correlations with patientspecific parameters. *Radiology, 277*(2), 471-476.

Purpose: To generate empirical sets of equations that can be used to calculate patient-specific organ doses resulting from a group of computed tomographic (CT) studies by using data from direct dose measurements performed within a human body. Materials and Methods: Organ dose

measurements were obtained in eight postmortem female subjects. A chest-abdomen-pelvis

protocol was used for this study. The relationships among measured organ doses, body mass

index, effective diameter (Deff), and volume CT dose index (CTDIvol) were investigated. Organ

dose equations were developed by means of linear regression from organ dose data, with

CTDIvol and Deff as variables, by using Pearson correlation coefficients and P values to determine

correlation strength of fit. Measured organ doses were compared with corresponding size-specific

dose estimates (SSDEs). Results: The central-section Deff presented similar correlations with

organ doses to those from Deff measured at specific organ locations. The strongest correlations

were observed between the central-section Deff and CTDIvol-normalized organ doses (R2: 0.478-

0.941). The average of measured organ doses for each subject resulted in an average difference

of only 5% from SSDE-calculated doses; however, individual organ doses differed from +31% to

261% from the calculated SSDE. Conclusion: The organ dose equations developed represent a

method for organ dose estimation from direct organ dose measurements that can estimate organ

doses more accurately than the calculated SSDE, which provides a less-specific patient dose

estimate. © 2015 RSNA.

Smedley, D., Jacobsen, J. O., Jager, M., Kohler, S., Holtgrewe, M., Schubach, M., et al. (2015). Next-
generation diagnostics and disease-gene discovery with the exomiser. *Nature Protocols, 10*(12),
2004-2015.

Exomiser is an application that prioritizes genes and variants in next-generation sequencing

(NGS) projects for novel disease-gene discovery or differential diagnostics of Mendelian disease.

Exomiser comprises a suite of algorithms for prioritizing exome sequences using random-walk

analysis of protein interaction networks, clinical relevance and cross-species phenotype

comparisons, as well as a wide range of other computational filters for variant frequency,

predicted pathogenicity and pedigree analysis. In this protocol, we provide a detailed explanation

of how to install Exomiser and use it to prioritize exome sequences in a number of scenarios.

Exomiser requires approximately 3 GB of RAM and roughly 15-90 s of computing time on a

standard desktop computer to analyze a variant call format (VCF) file. Exomiser is freely available

for academic use from http://www.sanger.ac.uk/science/tools/exomiser.

Smith, J. S., Lafage, V., Shaffrey, C. I., Schwab, F., Lafage, R., Hostin, R., et al. (2015). Outcomes of
operative and nonoperative treatment for adult spinal deformity: A prospective, multicenter,
propensity-matched cohort assessment with minimum 2-year follow-up. *Neurosurgery,*
BACKGROUND: High-quality studies that compare operative and nonoperative treatment for adult
spinal deformity (ASD) are needed. OBJECTIVE: To compare outcomes of operative and
nonoperative treatment for ASD. METHODS: This is a multicenter, prospective analysis of
consecutive ASD patients opting for operative or nonoperative care. Inclusion criteria were age
>18 years and ASD. Operative and nonoperative patients were propensity matched with the
baseline Oswestry Disability Index, Scoliosis Research Society-22r, thoracolumbar/lumbar Cobb
angle, pelvic incidence-to-lumbar lordosis mismatch (PI-LL), and leg pain score. Analyses were
confined to patients with a minimum of 2 years of follow-up. RESULTS: Two hundred eighty-six
operative and 403 nonoperative patients met the criteria, with mean ages of 53 and 55 years, 2-
year follow-up rates of 86% and 55%, and mean follow-up of 24.7 and 24.8 months,
respectively. At baseline, operative patients had significantly worse health-related quality of life
(HRQOL) based on all measures assessed (P /=1 complications. CONCLUSION: Operative
treatment for ASD can provide significant improvement of HRQOL at a minimum 2-year follow-
up. In contrast, nonoperative treatment on average maintains presenting levels of pain and
disability. ABBREVIATIONS: ASD, adult spinal deformityHRQOL, health-related quality of lifeLL,
lumbar lordosisMCID, minimal clinically important differenceNRS, numeric rating scaleODI,
Oswestry Disability IndexPI, pelvic incidenceSF-36, Short Form-36SRS-22r, Scoliosis Research
Society-22rSVA, sagittal vertical axis.

Sperber, H., Mathieu, J., Wang, Y., Ferreccio, A., Hesson, J., Xu, Z., et al. (2015). The metabolome
regulates the epigenetic landscape during naive-to-primed human embryonic stem cell transition.
Nature Cell Biology, 17(12), 1523-1535.
For nearly a century developmental biologists have recognized that cells from embryos can differ
in their potential to differentiate into distinct cell types. Recently, it has been recognized that
embryonic stem cells derived from both mice and humans exhibit two stable yet epigenetically
distinct states of pluripotency: naive and primed. We now show that nicotinamide N-
methyltransferase (NNMT) and the metabolic state regulate pluripotency in human embryonic

stem cells (hESCs). Specifically, in naive hESCs, NNMT and its enzymatic product 1-methylnicotinamide are highly upregulated, and NNMT is required for low S-adenosyl methionine (SAM) levels and the H3K27me3 repressive state. NNMT consumes SAM in naive cells, making it unavailable for histone methylation that represses Wnt and activates the HIF pathway in primed hESCs. These data support the hypothesis that the metabolome regulates the epigenetic landscape of the earliest steps in human development.

Stewart, M. P., Lorenz, A., Dahlman, J., & Sahay, G. (2015). Challenges in carrier-mediated intracellular delivery: Moving beyond endosomal barriers. *Wiley Interdisciplinary Reviews.Nanomedicine and Nanobiotechnology,*

The deployment of molecular to microscale carriers for intracellular delivery has tremendous potential for biology and medicine, especially for in vivo therapies. The field remains limited, however, by a poor understanding of how carriers gain access to the cell interior. In this review, we provide an overview of the different types of carriers, their speculated modes of entry, putative pathways of vesicular transport, and sites of endosomal escape. We compare this alongside pertinent examples from the cell biology of how viruses, bacteria, and their effectors enter cells and escape endosomal confinement. We anticipate insights into the mechanisms of cellular entry and endosomal escape will benefit future research efforts on effective carrier-mediated intracellular delivery. For further resources related to this article, please visit the WIREs website.

Stieglitz, E., Taylor-Weiner, A. N., Chang, T. Y., Gelston, L. C., Wang, Y. -., Mazor, T., et al. (2015). The genomic landscape of juvenile myelomonocytic leukemia. *Nature Genetics, 47*(11), 1326-1333.

Juvenile myelomonocytic leukemia (JMML) is a myeloproliferative neoplasm (MPN) of childhood with a poor prognosis. Mutations in NF1, NRAS, KRAS, PTPN11 or CBL occur in 85% of patients, yet there are currently no risk stratification algorithms capable of predicting which patients will be refractory to conventional treatment and could therefore be candidates for experimental therapies. In addition, few molecular pathways aside from the RAS-MAPK pathway have been identified that could serve as the basis for such novel therapeutic strategies. We therefore sought

to genomically characterize serial samples from patients at diagnosis through relapse and transformation to acute myeloid leukemia to expand knowledge of the mutational spectrum in JMML. We identified recurrent mutations in genes involved in signal transduction, splicing, Polycomb repressive complex 2 (PRC2) and transcription. Notably, the number of somatic alterations present at diagnosis appears to be the major determinant of outcome. © 2015 Nature America, Inc.

Streiff, C., Zhu, M., Panosian, J., Sahn, D. J., & Ashraf, M. (2015). Comprehensive evaluation of cardiac function and detection of myocardial infarction based on a semi-automated analysis using full-volume real time three-dimensional echocardiography. *Echocardiography (Mount Kisco, N.Y.)*, *32*(2), 332-338.

OBJECTIVE: Quantitative left ventricular mass (LVM) as well as regional strain values may be obtained from full-volume real time 3D echocardiography data via semi-automated feature tracking and represent indices of heart function, both in health and disease. METHODS: Fresh adult porcine and ovine hearts were passively pumped to simulate normal cardiac motion at stroke volumes (SVs) varying from 30 to 70 mL. A 3V-D Matrix probe, interfaced with a GE Vivid E9 ultrasound system, was used to image each heart at baseline conditions and after simulated myocardial infarction (MI). The 4D LV quantification function of EchoPAC PC was used to quantify the LVM and longitudinal and circumferential strain (LS & CS) of LV segments at each SV prior and subsequent to simulated MI. LVM was validated by volumetric displacement, while LS and CS values were compared to sonomicrometry-based strain. RESULTS: Linear regression analyses show excellent correlations in LVM, LS, and CS between the 4D echo and volumetric/sonomicrometric displacement with R^2 values of 0.99, 0.88, and 0.67, respectively. Bland-Altman analyses for all variables validate the compatibility of both methods. It was also determined that EchoPAC PC was able to detect a decrease in LS and CS in the relevant segments between pre- and post-MI at all SVs ($P < 0.05$). CONCLUSIONS: EchoPAC PC is a robust utility with the ability to accurately obtain quantitative LVM, LS, and CS values from 4D echo volumes and has the potential to improve the yield of clinical studies in cases of suspected MI.

Sudakin, D. (2015). Naltrexone: Not just for opioids anymore. *Journal of Medical Toxicology : Official Journal of the American College of Medical Toxicology,*
Naltrexone is a semi-synthetic opioid with competitive antagonist activity at mu opioid receptors. Its efficacy has been demonstrated in the treatment of alcohol and opioid dependence, but adherence to daily dosing has been recognized as a factor limiting long-term effectiveness. Recently, a long-acting injectable formulation of naltrexone has received FDA-approval for treating alcohol and opioid dependence. This article reviews the pharmacology of naltrexone, the current evidence supporting the use of extended-release naltrexone, and the clinical challenges in the induction of patients to this medication.

Sunstrom, R. E., & Langley, S. M. (2015). Reply. *The Annals of Thoracic Surgery, 100*(5), 1973-1974.

Tomita, G., Huang, D., O'Brien, C., Park, K. H., & Nakazawa, T. (2015). Ocular blood flow and visual function. *BioMed Research International, 2015*, 319254.

Tongue, J. R. (2015). Saline soliloquy: Shaking up our thoughts on perioperative hyponatremia: Commentary on an article by E. hennrikus, MD, et al.: "prevalence, timing, causes, and outcomes of hyponatremia in hospitalized orthopaedic surgery patients". *The Journal of Bone and Joint Surgery.American Volume, 97*(22), e74.

Traboulsee, A., Simon, J. H., Stone, L., Fisher, E., Jones, D. E., Malhotra, A., et al. (2015). Revised recommendations of the consortium of MS centers task force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. *AJNR.American Journal of Neuroradiology,*
An international group of neurologists and radiologists developed revised guidelines for standardized brain and spinal cord MR imaging for the diagnosis and follow-up of MS. A brain MR imaging with gadolinium is recommended for the diagnosis of MS. A spinal cord MR imaging is recommended if the brain MR imaging is nondiagnostic or if the presenting symptoms are at the level of the spinal cord. A follow-up brain MR imaging with gadolinium is recommended to demonstrate dissemination in time and ongoing clinically silent disease activity while on treatment, to evaluate unexpected clinical worsening, to re-assess the original diagnosis, and as

a new baseline before starting or modifying therapy. A routine brain MR imaging should be considered every 6 months to 2 years for all patients with relapsing MS. The brain MR imaging protocol includes 3D T1-weighted, 3D T2-FLAIR, 3D T2-weighted, post-single-dose gadolinium-enhanced T1-weighted sequences, and a DWI sequence. The progressive multifocal leukoencephalopathy surveillance protocol includes FLAIR and DWI sequences only. The spinal cord MR imaging protocol includes sagittal T1-weighted and proton attenuation, STIR or phase-sensitive inversion recovery, axial T2- or T2*-weighted imaging through suspicious lesions, and, in some cases, postcontrast gadolinium-enhanced T1-weighted imaging. The clinical question being addressed should be provided in the requisition for the MR imaging. The radiology report should be descriptive, with results referenced to previous studies. MR imaging studies should be permanently retained and available. The current revision incorporates new clinical information and imaging techniques that have become more available.

Truong, B., Rich-Garg, N., Ehst, B. D., Deodhar, A. A., Ku, J. H., Vakil-Gilani, K., et al. (2015). Demographics, clinical disease characteristics, and quality of life in a large cohort of psoriasis patients with and without psoriatic arthritis. *Clinical, Cosmetic and Investigational Dermatology, 8*, 563-569.

Innovation: What is already known about the topic: psoriasis (PsO) is a common skin disease with major impact on quality of life (QoL). Patient-reported data on QoL from large number of PsO patients with and without psoriatic arthritis (PsA) are limited. What this study adds: In a large cohort referred to a university psoriasis center, patients with PsO and concomitant PsA (~30% in this group) had greater degrees of skin and nail involvement and experienced greater negative impacts on QoL. Despite large numbers of patients with moderate-to-severe disease, use of systemic therapy by community practitioners was uncommon. Background: PsO and PsA are common diseases that have marked adverse impacts on QoL. The disease features and patient-reported QoL data comparing PsO and PsA patients are limited. Objective: To identify and compare demographics, clinical disease characteristics, and QoL scores in a large cohort of PsO patients with and without PsA. Methods: All PsO patients seen in a psoriasis specialty clinic, named the Center of Excellence for Psoriasis and Psoriatic Arthritis, were enrolled in an observational cohort. Demographic, QoL, and clinical data were collected from patient-reported

questionnaires and from physical examinations performed by Center of Excellence for Psoriasis and Psoriatic Arthritis dermatologists and a rheumatologists. Cross sectional descriptive data were collected and comparisons between patients with PsO alone and those with concomitant PsA are presented. Results: A total of 568 patients were enrolled in the database. Mean age of PsO onset was 28 years and mean disease duration was 18 years. Those with family history had an earlier onset of PsO by ~7 years. Mean body surface area involvement with PsO was 14%. Mean body mass index was 30.7. Prevalence of PsA was 29.8%. PsA patients had a higher mean body surface area compared to patients with PsO alone (16.7% vs 13.4%, P<0.05), higher prevalence of psoriatic nail changes (54.4% vs 36%, P<0.0002), and worse QoL scores as assessed by the Short Form-12 (67 vs 52, P<0.00001), Psoriasis Quality of Life-12 questionnaire (62 vs 71, P<0.01), and Routine Assessment of Patient Index Data 3 (2.3 vs 4.7, P<0.01). Strikingly, 49% of patients with PsO had never received any systemic therapy. Conclusion: These data highlight that PsO has marked negative impacts on QoL, while those patients with concomitant PsA are affected to a much greater degree. Despite large numbers of patients presenting with moderate-to-severe disease, use of systemic therapy for both PsO and PsA was uncommon. © 2015 Truong et al.

Tshala-Katumbay, D., Mwanza, J. C., Rohlman, D. S., Maestre, G., & Oria, R. B. (2015). A global perspective on the influence of environmental exposures on the nervous system. *Nature, 527*(7578), S187-92.

Economic transitions in the era of globalization warrant a fresh look at the neurological risks associated with environmental change. These are driven by industrial expansion, transfer and mobility of goods, climate change and population growth. In these contexts, risk of infectious and non-infectious diseases are shared across geographical boundaries. In low- and middle-income countries, the risk of environmentally mediated brain disease is augmented several fold by lack of infrastructure, poor health and safety regulations, and limited measures for environmental protection. Neurological disorders may occur as a result of direct exposure to chemical and/or non-chemical stressors, including but not limited to, ultrafine particulate matters. Individual susceptibilities to exposure-related diseases are modified by genetic, epigenetic and metagenomic factors. The existence of several uniquely exposed populations, including those in

the areas surrounding the Niger Delta or north western Amazon oil operations; those working in poorly regulated environments, such as artisanal mining industries; or those, mostly in sub-Saharan Africa, relying on cassava as a staple food, offers invaluable opportunities to advance the current understanding of brain responses to environmental challenges. Increased awareness of the brain disorders that are prevalent in low- and middle-income countries and investments in capacity for further environmental health-related research are positive steps towards improving human health.

Ventres, W. B. (2015). Building power between polarities: On the space-in-between. *Qualitative Health Research,*

In this article, I introduce the concept of the space-in-between. This space-in-between is born of the realization that, between the expression of any two polarities (across dimensions such as emotion, thought, geography, and ideology), there exists a philosophical construct useful for framing thinking about practice, research, and managerial relationships in the health professions. Out of this construct emerge practical considerations useful for structuring the conduct of meaningful interpersonal and intercultural interactions. I describe how the idea of a space-in-between developed out of my medical practice, grew as a result of my experiences in international environments. and has found fulfillment in my ongoing work. I explore the application of a space-in-between in public health, medical anthropology, medical ethics, and global health. I review how, as a result of incorporating this space in their daily work, clinicians, educators, researchers, and managers can grow as leaders by sharing the presence that arises from the space-in-between them and the people in the communities they serve.

Ventres, W. B. (2015). Where I practice: On the spaces of family medicine. *Journal of the American Board of Family Medicine : JABFM, 28*(6), 841-844.
In this essay, the author explores 3 distinct "spaces" that have helped him metaphorically map the nature of his work as a family physician. These "spaces" represent cultural, personal, and relational environments in which he has practiced over the course of >30 years since beginning medical school. They concern, respectively, the dominant culture of medicine, one core philosophy of family medicine (the biopsychosocialexistential model), and the development of

strong therapeutic bonds with patients. The author presents this textual and graphic exploration of "space" in hopes that others might reflect on their work, examine how they approach it, and bring richness and renewed meaning to their work as family physicians.

Vermehren-Schmaedick, A., Khanjian, R. A., & Balkowiec, A. (2015). Cellular mechanisms of activity-dependent BDNF expression in primary sensory neurons. *Neuroscience, 310*, 665-673. Brain-derived neurotrophic factor (BDNF) is abundantly expressed by both developing and adult rat visceral sensory neurons from the nodose ganglion (NG) in vivo and in vitro. We have previously shown that BDNF is released from neonatal NG neurons by activity and regulates dendritic development in their postsynaptic targets in the brainstem. The current study was carried out to examine the cellular and molecular mechanisms of activity-dependent BDNF expression in neonatal rat NG neurons, using our established in vitro model of neuronal activation by electrical field stimulation with patterns that mimic neuronal activity in vivo. We show that BDNF mRNA (transcript 4) increases over threefold in response to a 4-h tonic or bursting pattern delivered at the frequency of 6. Hz, which corresponds to the normal heart rate of a newborn rat. No significant increase in BDNF expression was observed following stimulation at 1. Hz. The latter effect suggests a frequency-dependent mechanism of regulated BDNF expression. In addition to BDNF transcript 4, which is known to be regulated by activity, transcript 1 also showed significant upregulation. The increases in BDNF mRNA were followed by BDNF protein upregulation of a similar magnitude after 24 h of stimulation at 6. Hz. Electrical stimulation-evoked BDNF expression was inhibited by pretreating neurons with the blocker of voltage-gated sodium channels tetrodotoxin and by removing extracellular calcium. Moreover, our data show that repetitive stimulation-evoked BDNF expression requires calcium influx through N-, but not L-type, channels. Together, our study reveals novel mechanisms through which electrical activity stimulates de novo synthesis of BDNF in sensory neurons, and points to the role of N-type calcium channels in regulating BDNF expression in sensory neurons in response to repetitive stimulation. © 2015 IBRO.

Wennergren, J. E., Askenasy, E. P., Greenberg, J. A., Holihan, J., Keith, J., Liang, M. K., et al. (2015). Laparoscopic ventral hernia repair with primary fascial closure versus bridged repair: A risk-

adjusted comparative study. *Surgical Endoscopy,*

BACKGROUND: Laparoscopy, specifically the bridged mesh technique, is a popular means used for ventral hernia repair. While laparoscopy has decreased the incidence of surgical site infection (SSI), hernia recurrence rates remain unchanged. Some surgeons advocate laparoscopic primary fascial closure (PFC) with placement of intraperitoneal mesh to decrease recurrence rates. We hypothesize that in patients undergoing laparoscopic ventral hernia repair (LVHR), PFC compared to a bridged mesh repair decreases hernia recurrence rates. METHODS: A multicenter, retrospective database of all ventral hernia repairs performed from 2010-2012 was accessed. Patients who underwent LVHR with mesh were reviewed. Patients who had PFC were compared to bridged repair. Primary outcome was hernia recurrence determined by clinical examination or CT scan. Secondary outcomes included SSI and seroma formation. RESULTS: A total of 1594 patients were identified. Following exclusion, a total of 196 patients were left who underwent LVHR with a mean follow-up period of 17.5 months. Ninety-seven patients underwent PFC, while 99 underwent bridged repairs. Initial comparisons between both groups was negative for any significant statistical difference in terms of recurrence, seroma formation, SSI, deep/organ space SSI, reoperation, and readmission. The same initial findings held true during subgroup analysis. Propensity score analysis was then performed for recurrence, seroma, and SSI controlling for age, gender, immune status, ASA class, BMI, smoking status, and acute repair. No statistically significant differences were identified in either group. CONCLUSION: Primary fascial closure during laparoscopic hernia repairs did not result in reduced recurrence, seroma, and SSI as compared to bridge repairs in a retrospective, multi-institutional study. However, additional research is needed to further evaluate benefits to the patient in terms of pain, function, cosmesis, and overall satisfaction. Randomized, blinded, control trials should focus on these parameters in future investigations.

Winters-Stone, K. M., Bennett, J., & Mick, D. (2015). Preventing frailty in older cancer survivors. *Topics in Geriatric Rehabilitation, 31*(4), 241-245.

Emerging data suggest that cancer treatments can accelerate the aging process in older cancer survivors, increasing their risk for developing frailty, a state of aging that implies an increasing vulnerability to stressors. Frailty may explain the greater level of disability, increased fall risk,

lower physical functioning, and increased mortality in cancer survivors relative to their healthy peers. Obviously, reducing frailty would be of benefit to the cancer survivor, and exercise training may hold promise as a therapeutic approach to reducing frailty in older cancer survivors. The purpose of this review was to summarize the current understanding of (1) the linkages between cancer, cancer treatment, and the development of frailty; and (2) the role that exercise training might play in reducing this condition.

Winthrop, K., Rivera, A., Engelmann, F., Rose, S., Lewis, A., Ku, J., et al. (2015). A rhesus macaque model of pulmonary nontuberculous mycobacterial disease. *American Journal of Respiratory Cell and Molecular Biology,*
In this study, we sought to develop a nonhuman primate model of pulmonary Mycobacterium avium complex (MAC) disease. Blood and bronchial alveolar lavage were collected from three female rhesus macaques infected intrabronchially with escalating doses of Mycobacterium avium hominissuis. Immunity was determined by measuring cytokine levels, lymphocyte proliferation and antigen-specific responses. Disease progression was monitored clinically and microbiologically with serial thoracic radiographs, computed tomography scans and quantitative mycobacterial cultures. The animal subjected to the highest inoculum showed evidence of chronic pulmonary MAC disease. Therefore, rhesus macaques could provide a robust model in which to investigate host-pathogen interactions during MAC infection.

Woltjer, R. L., Reese, L. C., Richardson, B. E., Tran, H., Green, S., Pham, T., et al. (2015). Pallidal neuronal apolipoprotein E in pantothenate kinase-associated neurodegeneration recapitulates ischemic injury to the globus pallidus. *Molecular Genetics and Metabolism,*
Pantothenate kinase-associated neurodegeneration (PKAN) is a progressive movement disorder that is due to mutations in PANK2. Pathologically, it is a member of a class of diseases known as neurodegeneration with brain iron accumulation (NBIA) and features increased tissue iron and ubiquitinated proteinaceous aggregates in the globus pallidus. We have previously determined that these aggregates represent condensed residue derived from degenerated pallidal neurons. However, the protein content, other than ubiquitin, of these aggregates remains unknown. In the

present study, we performed biochemical and immunohistochemical studies to characterize these aggregates and found them to be enriched in apolipoprotein E that is poorly soluble in detergent solutions. However, we did not determine a significant association between APOE genotype and the clinical phenotype of disease in our database of 81 cases. Rather, we frequently identified similar ubiquitin- and apolipoprotein E-enriched lesions in these neurons in non-PKAN patients in the penumbrae of remote infarcts that involve the globus pallidus, and occasionally in other brain sites that contain large gamma-aminobutyric acid (GABA)ergic neurons. Our findings, taken together, suggest that tissue or cellular hypoxic/ischemic injury within the globus pallidus may underlie the pathogenesis of PKAN.

Wright, K. M., Lyon, K., & Ginty, D. (2015). Dystroglycan is a critical regulator of forebrain connectivity. *International Journal of Developmental Neuroscience : The Official Journal of the International Society for Developmental Neuroscience, 47*(Pt A), 117.

Yao, H., Ferdaus, M. Z., Md. Zahid, H., Ohara, H., Nakahara, T., & Nabika, T. (2015). Focal ischemic injury with complex middle cerebral artery in stroke-prone spontaneously hypertensive rats with loss-of-function in NADPH oxidases. *Plos One, 10*(9)

By means of introgressing a loss-of-function mutation in the p22phox gene from the Matsumoto Eosinophilia Shinshu (MES) rat to stroke-prone spontaneously hypertensive rats (SHRSP), we constructed the SHRSP-based congenic strain lacking the P22PHOX expression (i.e., lacking NADPH oxidases [NOX] activities) (SHRSP.MES-Cybames/Izm; hereafter referred to as SP.MES). To examine the effects of Nox activities on the focal ischemic injury or stroke, we performed middle cerebral artery (MCA) occlusion in this new congenic strain; the distal MCA was occluded by 561-nm laser-driven photothrombosis. Resting mean arterial blood pressure was significantly lower in SP.MES when compared with the control PM0/SHRSP (150 ± 11 mmHg vs. 166 ± 11 mmHg). Cerebral blood flow decreased to $37 \pm 13\%$ in SP.MES and $35 \pm 17\%$ in PM0/SHRSP at 10 min after MCA occlusion (not significant). Infarct volume determined at 24 h after MCA occlusion in SP.MES was 89 ± 39 mm3, which was not significantly different from 83 ± 35 mm3 in PM0/SHRSP. The distal MCA pattern was more complex in SP.MES (median 3, IQR 3-5) than PM0/SHRSP (median 2, IQR 1-3) ($p = 0.001$). Because more complex distal MCA is known to

produce larger infarction after distal MCA occlusion in SHR, we adjusted for the branching pattern in an ANCOVA. The adjusted mean of infarct volume was significantly smaller in SP.MES compared with that in PM0/ SHRSP (67 [95% CI 46 to 87] mm3 vs. 100 [95% CI 82 to 118] mm3, p = 0.032). Elimination of the P22PHOX expression induced complex distal MCA, which would suggest the presence of 'loss of complexity' induced by enhanced oxidative stress in SHRSP; infarct size in SP.MES-when adjusted for distal MCA complexity-was significantly attenuated compared with that in PM0/SHRSP. Therefore, the present results suggest that Nox is harmful for ischemic brain tissue. Copyright: © 2015 Yao et al.

Yorgason, J. T., Calipari, E. S., Ferris, M. J., Karkhanis, A. N., Fordahl, S. C., Weiner, J. L., et al. (2015). Social isolation rearing increases dopamine uptake and psychostimulant potency in the striatum. *Neuropharmacology, 101*, 471-479.

Social isolation rearing (SI) is a model of early life stress that results in neurobiological alterations leading to increased anxiety-like behaviors. These animals also exhibit an increased propensity to administer psychostimulants, such as cocaine; however, the mechanisms governing this increased addiction vulnerability remain to be elucidated. Long-term stressors have been shown to produce important alterations in nucleus accumbens core (NAc) function. The NAc regulates motivated and goal-directed behaviors, and individual differences in NAc function have been shown to be predictive of addiction vulnerability. Rats were reared in group (GH; 4/cage) or SI (1/cage) conditions from weaning (PD 28) into early adulthood (PD 77) and dopamine release was assessed using voltammetry in brain slices containing the NAc and dorsomedial striatum. SI rats exhibited enhanced dopamine release and uptake in both regions compared to GH rats. In regard to psychostimulant effects directly at the dopamine transporter (DAT), methylphenidate and amphetamine, but not cocaine, inhibited uptake more in SI than GH rats. The increased potencies were positively correlated with uptake rates, suggesting that increased potencies of amphetamine-like compounds are due to changes in DAT function. Cocaine's effects on uptake were similar between rearing conditions, however, cocaine enhanced evoked dopamine release greater in SI than GH rats, suggesting that the enhanced cocaine reinforcement in SI animals involves a DAT independent mechanism. Together, the results provide the first evidence that

greater psychostimulant effects in SI compared to GH rats are due to effects on dopamine terminals related to uptake dependent and independent mechanisms.

Zabriskie, M. S., Eide, C. A., Yan, D., Vellore, N. A., Pomicter, A. D., Savage, S. L., et al. (2015). Extreme mutational selectivity of axitinib limits its potential use as a targeted therapeutic for BCR-ABL1-positive leukemia. *Leukemia,*

Zhu, M., Streiff, C., Panosian, J., Zhang, Z., Song, X., Sahn, D. J., et al. (2015). Regional strain determination and myocardial infarction detection by three-dimensional echocardiography with varied temporal resolution. *Echocardiography (Mount Kisco, N.Y.), 32*(2), 339-348. BACKGROUND: Three-dimensional echocardiography (3DE) is a promising method for strain determination; however, there are temporal resolution concerns. This study aims to evaluate the feasibility and accuracy of 3DE on longitudinal and circumferential strain (LS, CS) determination and infarction detection under variable frame rates (FR) and "heart rates" (stroke rates [SR]) conditions. METHODS: Latex balloons were sewn into the left ventricle (LV) of 20 freshly harvested pig hearts which were then passively driven by a pulsatile pump apparatus at stroke volumes (SV) 30-70 mL. The hearts were pumped at 2 normal limits of human heart rate. Full-volume data were acquired before and after a simulated myocardial infarction (MI) at the 2 most commonly used FRs. LS and CS values were evaluated against sonomicrometry. RESULTS: Longitudinal strain and CS derived from high FR acquisitions showed statistically superior correlations with sonomicrometry data (LS: $R(2) = 0.85$, CS: $R(2) = 0.84$) than strain values from low FR (LS: $R(2) = 0.78$, CS: $R(2) = 0.76$) (all $P < 0.01$). After MI induction, LS and CS at different FRs were significantly decreased while maintaining excellent correlations with sonomicrometry data (all $P < 0.001$). There is no statistical difference of strain values between different SR acquisitions. CONCLUSION: Three-dimensional wall-motion tracking has the ability to accurately determine regional myocardial deformation and detect MI. Different heart rates within a physiologically relevant range have no effect on 3D strain accuracy. Strain values calculated from higher frame rate acquisitions were found to have a slightly better accuracy.

Zuloaga, D. G., Johnson, L. A., Weber, S., & Raber, J. (2015). Immediate and lasting effects of chronic daily methamphetamine exposure on activation of cells in hypothalamic-pituitary-adrenal axis-

associated brain regions. *Psychopharmacology,*

RATIONALE: Chronic methamphetamine (MA) abuse leads to dependence and symptoms of withdrawal after use has ceased. Negative mood states associated with withdrawal, as well as drug reinstatement, have been linked to drug-induced disruption of the hypothalamic-pituitary-adrenal (HPA) axis. However, effects of chronic MA exposure or acute MA exposure following withdrawal on neural activation patterns within brain regions that regulate the HPA axis are unknown. OBJECTIVES: In this study, neural activation patterns were assessed by quantification of c-Fos protein in mice exposed to different regimens of MA administration. METHODS: (Experiment 1) Adult male mice were treated with MA (5 mg/kg) or saline once or once daily for 10 days. (Experiment 2) Mice were treated with MA or saline once daily for 10 days and following a 10-day withdrawal period were re-administered a final dose of MA or saline. c-Fos was quantified in brains after the final injection. RESULTS: (Experiment 1) Compared to exposure to a single dose of MA (5 mg/kg), chronic MA exposure decreased the number of c-Fos expressing cells in the paraventricular hypothalamus, dorsomedial hypothalamus, central amygdala, basolateral amygdala, bed nucleus of the stria terminalis (BNST), and CA3 hippocampal region. (Experiment 2) Compared to mice receiving their first dose of MA, mice chronically treated with MA, withdrawn, and re-administered MA, showed decreased c-Fos expressing cells within the central and basolateral amygdala, BNST, and CA3. CONCLUSIONS: HPA axis-associated amygdala, extended amygdala, and hippocampal regions endure lasting effects following chronic MA exposure and therefore may be linked to stress-related withdrawal symptoms.