References

Achenbach, S., Einstein, A. J., & Ferencik, M. (2015). How much evidence is in a case report? A road trip of scientific evidence, including skeptics, ockham's razor, hume's fork, and karl R. popper. *Journal of Cardiovascular Computed Tomography, 9*(4), 267-269.

Agarwal, A., Mackenzie, R. J., Eide, C. A., Davare, M. A., Watanabe-Smith, K., Tognon, C. E., et al. (2015). Functional RNAi screen targeting cytokine and growth factor receptors reveals oncorequisite role for interleukin-2 gamma receptor in JAK3-mutation-positive leukemia. *Oncogene, 34*(23), 2991-2999.

To understand the role of cytokine and growth factor receptor-mediated signaling in leukemia pathogenesis, we designed a functional RNA interference (RNAi) screen targeting 188 cytokine and growth factor receptors that we found highly expressed in primary leukemia specimens. Using this screen, we identified interleukin-2 gamma receptor (IL2Rγ) as a critical growth determinant for a JAK3 A572V mutation-positive acute myeloid leukemia cell line. We observed that knockdown of IL2Rγ abrogates phosphorylation of JAK3 and downstream signaling molecules, JAK1, STAT5, MAPK and pS6 ribosomal protein. Overexpression of IL2Rγ in murine cells increased the transforming potential of activating JAK3 mutations, whereas absence of IL2Rγ completely abrogated the clonogenic potential of JAK3 A572V, as well as the transforming potential of additional JAK3-activating mutations such as JAK3 M511I. In addition, mutation at the IL2Rγ interaction site in the FERM domain of JAK3 (Y100C) completely abrogated JAK3-mediated leukemic transformation. Mechanistically, we found IL2Rγ contributes to constitutive JAK3 mutant signaling by increasing JAK3 expression and phosphorylation. Conversely, we found that mutant, but not wild-type JAK3, increased the expression of IL2Rγ, indicating IL2Rγ and JAK3 contribute to constitutive JAK/STAT signaling through their reciprocal regulation. Overall, we demonstrate a novel role for IL2Rγ in potentiating oncogenesis in the setting of JAK3-mutation-positive leukemia. In addition, our study highlights an RNAi-based functional assay that can be used to facilitate the identification of non-kinase cytokine and growth factor receptor targets for inhibiting leukemic cell growth. © 2015 Macmillan Publishers Limited.

Ambrosone, C. B., Zirpoli, G., Hong, C. C., Yao, S., Troester, M. A., Bandera, E. V., et al. (2015). Important role of menarche in development of estrogen receptor-negative breast cancer in african american women. *Journal of the National Cancer Institute*, *107*(9), 10.1093/jnci/djv172. Print 2015 Sep.

BACKGROUND: Menarche is a critical time point for diverging fates of mammary cells of origin. African American women have young age at menarche, which could be associated with their high rates of estrogen receptor-negative (ER-) breast cancer. METHODS: In the AMBER Consortium, using harmonized data from 4426 African American women with breast cancer and 17 474 controls, we used polytomous logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for ages at menarche and first live birth (FLB), and the interval between, in relation to ER+ and ER- breast cancer. All statistical tests were two-sided. RESULTS: Risk of ER- breast cancer was reduced with later age at menarche among both parous and nulliparous women (>/=15 vs <11 years OR = 0.62, 95% CI = 0.48 to 0.81 and OR = 0.56, 95% CI = 0.29 to 1.10, respectively), with no effect of age at FLB. For ER+ breast cancer, the inverse association was weaker among nulliparous women. While longer intervals between menarche and FLB were associated with increased risk of ER+ breast cancer in a dose-response fashion (OR for 20 year interval = 1.39, 95% CI = 1.08 to 1.79, P trend = .003), ER- risk was only increased for intervals up to 14 years and not beyond (P trend = .33). CONCLUSIONS: While ER- breast cancer risk was markedly reduced in women with a late age at menarche, there was not a clear pattern of increased risk with longer interval between menarche and FLB, as was observed for ER+ breast cancer. These findings indicate that etiologic pathways involving adolescence and pregnancy may differ for ER- and ER+ breast cancer.

Ananthakrishnan, A. N., & Lieberman, D. (2015). Patient electronic health records as a means to approach genetic research in gastroenterology. *Gastroenterology*,

Electronic health records (EHR) are being increasingly utilized and form a unique source of extensive data gathered during routine clinical care. Through use of codified and free text concepts identified using clinical informatics tools, disease labels can be assigned with a high degree of accuracy. Analysis linking such EHR-assigned disease labels to a biospecimen repository has demonstrated that genetic associations identified in prospective cohorts can be

replicated with adequate statistical power, and novel phenotypic associations identified. In addition, genetic discovery research can be performed utilizing clinical, laboratory, and procedure data obtained during care. Challenges with such research include the need to tackle variability in quality and quantity of EHR data and importance of maintaining patient privacy and data security. With appropriate safeguards, this novel and emerging field of research offers considerable promise and potential to further scientific research in gastroenterology efficiently, cost-effectively, and with engagement of patients and communities.

Attenberger, U., Catana, C., Chandarana, H., Catalano, O. A., Friedman, K., Schonberg, S. A., et al. (2015). Whole-body FDG PET-MR oncologic imaging: Pitfalls in clinical interpretation related to inaccurate MR-based attenuation correction. *Abdominal Imaging*,
Simultaneous data collection for positron emission tomography and magnetic resonance imaging (PET/MR) is now a reality. While the full benefits of concurrently acquiring PET and MR data and the potential added clinical value are still being evaluated, initial studies have identified several important potential pitfalls in the interpretation of fluorodeoxyglucose (FDG) PET/MRI in oncologic whole-body imaging, the majority of which being related to the errors in the attenuation maps created from the MR data. The purpose of this article was to present such pitfalls and artifacts using case examples, describe their etiology, and discuss strategies to overcome them. Using a case-based approach, we will illustrate artifacts related to (1) Inaccurate bone tissue segmentation; (2) Inaccurate air cavities segmentation; (3) Motion-induced misregistration; (4) RF coils in the PET field of view; (5) B0 field inhomogeneity; (6) B1 field inhomogeneity; (7) Metallic implants; (8) MR contrast agents. © 2015 Springer Science+Business Media New York

Atwell, L. L., Beaver, L. M., Shannon, J., Williams, D. E., Dashwood, R. H., & Ho, E. (2015). Epigenetic regulation by sulforaphane: Opportunities for breast and prostate cancer chemoprevention. *Current Pharmacology Reports, 1*(2), 102-111.
Sulforaphane (SFN) is a phytochemical derived from cruciferous vegetables that has multiple molecular targets and anti-cancer properties. Researchers have demonstrated several chemopreventive benefits of SFN consumption, such as reductions in tumor growth, increases in cancer cell apoptosis, and disruption of signaling within tumor microenvironments both in vitro

and in vivo. Emerging evidence indicates that SFN exerts several of its chemopreventive effects by altering epigenetic mechanisms. This review summarizes evidence of the impact of SFN on epigenetic events and how they relate to the chemopreventive effects of SFN observed in preclinical and clinical studies of breast and prostate cancers. Specific areas of focus include the role of SFN in the regulation of cell cycle, apoptosis, inflammation, antioxidant defense, and cancer cell signaling and their relationships to epigenetic mechanisms. Finally, remaining challenges and research needs for translating mechanistic work with SFN into human studies and clinical intervention trials are discussed.

Atzmony, L., Hodak, E., Leshem, Y. A., Rosenbaum, O., Gdalevich, M., Anhalt, G. J., et al. (2015). The role of adjuvant therapy in pemphigus: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*,

BACKGROUND: The assumption that adjuvant modalities have added value to oral glucocorticoids in the treatment of pemphigus is intuitively sound but has not been conclusively proven. OBJECTIVE: We sought to compare the efficacy and safety of oral glucocorticoid treatment with or without adjuvants for pemphigus vulgaris and pemphigus foliaceus. METHODS: We performed a systematic review and meta-analysis of randomized controlled trials. The primary outcome was remission. Secondary outcomes were disease control, time to disease control, relapse, time to relapse, cumulative glucocorticoid dose, withdrawal because of adverse events, and all-cause death. Trials were pooled irrespective of adjuvant type evaluated. RESULTS: Ten trials (559 participants) were included. Adjuvants evaluated were azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, intravenous immunoglobulin, plasma exchange, and infliximab; not all were included in every analysis. Although adjuvants were not beneficial for achieving remission, they were found to collectively decrease the risk of relapse by 29% (relative risk 0.71, 95% confidence interval 0.53-0.95). LIMITATIONS: Different adjuvants were pooled together. CONCLUSION: Adjuvants have a role in pemphigus treatment, at least in reducing the risk of relapse. Further randomized controlled trials of other promising modalities are warranted.

Austin, J. P. (2015). Trickle-down professionalism: Hidden curriculum and the pediatric hospitalist. *Hospital Pediatrics*, *5*(6), 352-354.

Ayton, S., Faux, N. G., Bush, A. I., Weiner, M. W., Aisen, P., Petersen, R., et al. (2015). Ferritin levels in the cerebrospinal fluid predict alzheimer's disease outcomes and are regulated by APOE. *Nature Communications, 6*

Brain iron elevation is implicated in Alzheimer's disease (AD) pathogenesis, but the impact of iron on disease outcomes has not been previously explored in a longitudinal study. Ferritin is the major iron storage protein of the body; by using cerebrospinal fluid (CSF) levels of ferritin as an index, we explored whether brain iron status impacts longitudinal outcomes in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. We show that baseline CSF ferritin levels were negatively associated with cognitive performance over 7 years in 91 cognitively normal, 144 mild cognitive impairment (MCI) and 67 AD subjects, and predicted MCI conversion to AD. Ferritin was strongly associated with CSF apolipoprotein E levels and was elevated by the Alzheimer's risk allele, APOE-ε4. These findings reveal that elevated brain iron adversely impacts on AD progression, and introduce brain iron elevation as a possible mechanism for APOE-ε4 being the major genetic risk factor for AD. © 2015 Macmillan Publishers Limited. All rights reserved.

Bachmann-Gagescu, R., Dempsey, J. C., Phelps, I. G., O'Roak, B. J., Knutzen, D. M., Rue, T. C., et al. (2015). Joubert syndrome: A model for untangling recessive disorders with extreme genetic heterogeneity. *Journal of Medical Genetics,*

BACKGROUND: Joubert syndrome (JS) is a recessive neurodevelopmental disorder characterised by hypotonia, ataxia, cognitive impairment, abnormal eye movements, respiratory control disturbances and a distinctive mid-hindbrain malformation. JS demonstrates substantial phenotypic variability and genetic heterogeneity. This study provides a comprehensive view of the current genetic basis, phenotypic range and gene-phenotype associations in JS. METHODS: We sequenced 27 JS-associated genes in 440 affected individuals (375 families) from a cohort of 532 individuals (440 families) with JS, using molecular inversion probe-based targeted capture and next-generation sequencing. Variant pathogenicity was defined using the Combined Annotation Dependent Depletion algorithm with an optimised score cut-off. RESULTS: We identified presumed causal variants in 62% of pedigrees, including the first B9D2 mutations associated with JS. 253 different mutations in 23 genes highlight the extreme genetic heterogeneity of JS. Phenotypic analysis revealed that only 34% of individuals have a 'pure JS'

phenotype. Retinal disease is present in 30% of individuals, renal disease in 25%, coloboma in 17%, polydactyly in 15%, liver fibrosis in 14% and encephalocele in 8%. Loss of CEP290 function is associated with retinal dystrophy, while loss of TMEM67 function is associated with liver fibrosis and coloboma, but we observe no clear-cut distinction between JS subtypes. CONCLUSIONS: This work illustrates how combining advanced sequencing techniques with phenotypic data addresses extreme genetic heterogeneity to provide diagnostic and carrier testing, guide medical monitoring for progressive complications, facilitate interpretation of genome-wide sequencing results in individuals with a variety of phenotypes and enable gene-specific treatments in the future.

Bajaj Pahuja, K., Wang, J., Blagoveshchenskaya, A., Lim, L., Madhusudhan, M. S., Mayinger, P., et al. (2015). Phosphoregulatory protein 14-3-3 facilitates SAC1 transport from the endoplasmic reticulum. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(25), E3199-206.

Most secretory cargo proteins in eukaryotes are synthesized in the endoplasmic reticulum and actively exported in membrane-bound vesicles that are formed by the cytosolic coat protein complex II (COPII). COPII proteins are assisted by a variety of cargo-specific adaptor proteins required for the concentration and export of secretory proteins from the endoplasmic reticulum (ER). Adaptor proteins are key regulators of cargo export, and defects in their function may result in disease phenotypes in mammals. Here we report the role of 14-3-3 proteins as a cytosolic adaptor in mediating SAC1 transport in COPII-coated vesicles. Sac1 is a phosphatidyl inositol-4 phosphate (PI4P) lipid phosphatase that undergoes serum dependent translocation between the endoplasmic reticulum and Golgi complex and controls cellular PI4P lipid levels. We developed a cell-free COPII vesicle budding reaction to examine SAC1 exit from the ER that requires COPII and at least one additional cytosolic factor, the 14-3-3 protein. Recombinant 14-3-3 protein stimulates the packaging of SAC1 into COPII vesicles and the sorting subunit of COPII, Sec24, interacts with 14-3-3. We identified a minimal sorting motif of SAC1 that is important for 14-3-3 binding and which controls SAC1 export from the ER. This LS motif is part of a 7-aa stretch, RLSNTSP, which is similar to the consensus 14-3-3 binding sequence. Homology models, based on the SAC1 structure from yeast, predict this region to be in the exposed exterior of the protein.

Our data suggest a model in which the 14-3-3 protein mediates SAC1 traffic from the ER through direct interaction with a sorting signal and COPII.

Baker-Groberg, S. M., Phillips, K. G., Healy, L. D., Itakura, A., Porter, J. E., Newton, P. K., et al. (2015). Critical behavior of subcellular density organization during neutrophil activation and migration. *Cellular and Molecular Bioengineering,*

Physical theories of active matter continue to provide a quantitative understanding of dynamic cellular phenomena, including cell locomotion. Although various investigations of the rheology of cells have identified important viscoelastic and traction force parameters for use in these theoretical approaches, a key variable has remained elusive both in theoretical and experimental approaches: the spatiotemporal behavior of the subcellular density. The evolution of the subcellular density has been qualitatively observed for decades as it provides the source of image contrast in label-free imaging modalities (e.g., differential interference contrast, phase contrast) used to investigate cellular specimens. While these modalities directly visualize cell structure, they do not provide quantitative access to the structures being visualized. We present an established quantitative imaging approach, non-interferometric quantitative phase microscopy, to elucidate the subcellular density dynamics in neutrophils undergoing chemokinesis following uniform bacterial peptide stimulation. Through this approach, we identify a power law dependence of the neutrophil mean density on time with a critical point, suggesting a critical density is required for motility on 2D substrates. Next we elucidate a continuum law relating mean cell density, area, and total mass that is conserved during neutrophil polarization and migration. Together, our approach and quantitative findings will enable investigators to define the physics coupling cytoskeletal dynamics with subcellular density dynamics during cell migration.

Baquero, A. F., Kirigiti, M. A., Baquero, K. C., Lee, S. J., Smith, M. S., & Grove, K. L. (2015). Developmental changes in synaptic distribution in arcuate nucleus neurons. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 35*(22), 8558-8569.

Neurons coexpressing neuropeptide Y, agouti-related peptide, and GABA (NAG) play an important role in ingestive behavior and are located in the arcuate nucleus of the hypothalamus. NAG

neurons receive both GABAergic and glutamatergic synaptic inputs, however, the developmental time course of synaptic input organization of NAG neurons in mice is unknown. In this study, we show that these neurons have low numbers of GABAergic synapses and that GABA is inhibitory to NAG neurons during early postnatal period. In contrast, glutamatergic inputs onto NAG neurons are relatively abundant by P13 and are comparatively similar to the levels observed in the adult. As mice reach adulthood (9-10 weeks), GABAergic tone onto NAG neurons increases. At this age, NAG neurons received similar numbers of inhibitory and EPSCs. To further differentiate age-associated changes in synaptic distribution, 17- to 18-week-old lean and diet-induced obesity (DIO) mice were studied. Surprisingly, NAG neurons from lean adult mice exhibit a reduction in the GABAergic synapses compared with younger adults. Conversely, DIO mice display reductions in the number of GABAergic and glutamatergic inputs onto NAG neurons. Based on these experiments, we propose that synaptic distribution in NAG neurons is continuously restructuring throughout development to accommodate the animals' energy requirements.

Bascom, P. B. (2014). "Вода". *Journal of Palliative Medicine, 17*(9), 1068-1069.

Basso, L. R., Gast, C. E., Bruzual, I., & Wong, B. (2014). Identification and properties of plasma membrane azole efflux pumps from the pathogenic fungi cryptococcus gattii and cryptococcus neoformans. *Journal of Antimicrobial Chemotherapy, 70*(5), 1396-1407.
Objectives: Cryptococcus gattii from the North American Northwest (NW) have higher azole MICs than do non- NW C. gattii or Cryptococcus neoformans. Since mechanisms of azole resistance in C. gattii are not known, we identified C. gattii and C. neoformans plasma membrane azole efflux pumps and characterized their properties. Methods: The C. gattii R265 genome was searched for orthologues of known fungal azole efflux genes, expression of candidate genes was assessed by RT-PCR and the expressed genes' cDNAs were cloned and expressed in Saccharomyces cerevisiae. Azole MICs and intracellular [3H]fluconazole were measured in C. gattii and C. neoformans and in S. cerevisiae expressing each cDNA of interest, as was [3H]fluconazole uptake by post- Golgi vesicles (PGVs) isolated from S. cerevisiae sec6-4 mutants expressing each cDNA of interest. Results: Intracellular [3H]fluconazole concentrations were inversely correlated with fluconazole MICs only in 25 NW C. gattii strains. S. cerevisiae expressing three C. gattii cDNAs

(encoded by orthologues of C. neoformans AFR1 and MDR1 and the previously unstudied gene AFR2) and their C. neoformans counterparts had higher azole MICs and lower intracellular [3H]fluconazole concentrations than did empty-vector controls. PGVs from S. cerevisiae expressing all six Cryptococcus cDNAs also accumulated more [3H]fluconazole than did controls, and [3H]fluconazole transport by all six transporters of interest was ATP dependent and was inhibited by excess unlabelled fluconazole, voriconazole, itraconazole and posaconazole. Conclusions: We conclude that C. gattii and C. neoformans AFR1, MDR1 and AFR2 encode ABC transporters that pump multiple azoles out of S. cerevisiae cells, thereby causing azole resistance.

Beach, M. C., Roter, D. L., Saha, S., Korthuis, P. T., Eggly, S., Cohn, J., et al. (2015). Impact of a brief patient and provider intervention to improve the quality of communication about medication adherence among HIV patients. *Patient Education and Counseling*,

INTRODUCTION: Medication adherence is essential in HIV care, yet provider communication about adherence is often suboptimal. We designed this study to improve patient-provider communication about HIV medication adherence. METHODS: We randomized 26 providers at three HIV care sites to receive or not receive a one-hour communication skills training based on motivational interviewing principles applied to medication adherence. Prior to routine office visits, non-adherent patients of providers who received the training were coached to discuss adherence with their providers. Patients of providers who did not receive the training providers were not coached. We audio-recorded and coded patient-provider interactions using the roter interaction analysis system (RIAS). RESULTS: There was more dialogue about therapeutic regimen in visits with intervention patients and providers (167 vs 128, respectively, p=.004), with the majority of statements coming from providers. These visits also included more brainstorming solutions to nonadherence (41% vs. 22%, p=0.026). Intervention compared with control visit providers engaged in more positive talk (44 vs. 38 statements, p=0.039), emotional talk (26 vs. 18 statements, p<0.001), and probing of patient opinion (3 vs. 2 statements, p=0.009). CONCLUSION: A brief provider training combined with patient coaching sessions, improved provider communication behaviors and increased dialogue regarding medication adherence.

Benedek, G., Meza-Romero, R., Jordan, K., Keenlyside, L., Offner, H., & Vandenbark, A. A. (2015). HLA-DRalpha1-mMOG-35-55 treatment of experimental autoimmune encephalomyelitis reduces CNS inflammation, enhances M2 macrophage frequency, and promotes neuroprotection. *Journal of Neuroinflammation*, *12*, 123-015-0342-4.

BACKGROUND: DRalpha1-mouse(m)MOG-35-55, a novel construct developed in our laboratory as a simpler and potentially less immunogenic alternative to two-domain class II constructs, was shown previously to target the MIF/CD74 pathway and to reverse clinical and histological signs of experimental autoimmune encephalomyelitis (EAE) in DR*1501-Tg mice in a manner similar to the parent DR2beta1-containing construct. METHODS: In order to determine whether DRalpha1-mMOG-35-55 could treat EAE in major histocompatibility complex (MHC)-mismatched mice and to evaluate the treatment effect on central nervous system (CNS) inflammation, C57BL/6 mice were treated with DRalpha1-mMOG-35-55. In addition, gene expression profile was analyzed in spinal cords of EAE DR*1501-Tg mice that were treated with DRalpha1-mMOG-35-55. RESULTS: We here demonstrate that DRalpha1-mMOG-35-55 could effectively treat EAE in MHC-mismatched C57BL/6 mice by reducing CNS inflammation, potentially mediated in part through an increased frequency of M2 monocytes in the spinal cord. Microarray analysis of spinal cord tissue from DRalpha1-mMOG-35-55-treated vs. vehicle control mice with EAE revealed decreased expression of a large number of pro-inflammatory genes including CD74, NLRP3, and IL-1beta and increased expression of genes involved in myelin repair (MBP) and neuroregeneration (HUWE1). CONCLUSION: These findings indicate that the DRalpha1-mMOG-35-55 construct retains therapeutic, anti-inflammatory, and neuroprotective activities during treatment of EAE across MHC disparate barriers.

Bethea, C. L., Phu, K., Kim, A., & Reddy, A. P. (2015). Androgen metabolites impact CSF amines and axonal serotonin via MAO-A and -B in male macaques. *Neuroscience*,

A significant body of the literature has found that mutations or deletions of the monoamine oxidase-A (MAO-A) gene cause elevated CNS serotonin and elevated impulsive aggression in humans and animal models. In addition, low cerebrospinal fluid (CSF) 5-hydroxyindole acetic acid (5HIAA) has been documented in a limited number of violent criminal populations and in macaques that exhibit impulsive aggression. To reconcile these different analyses, we

hypothesized that CSF 5HIAA reflected degradation of serotonin by the activity of MAO-A; and that low MAO-A activity would result in lower CSF 5HIAA, but overall higher serotonin in the CNS. To test this hypothesis, male Japanese macaques (Macaca fuscata) were castrated, rested for 5-7months, and then treated for 3months with [1] placebo, [2] testosterone (T), [3] dihydrotestosterone (DHT; non-aromatizable androgen) and 1,4,6-androstatriene-3,17-dione (ATD) (steroidal aromatase inhibitor), or [4] flutamide (FLUT; androgen antagonist) and ATD (n=5/group). These treatments enable isolation of androgen and estrogen activities. In the dorsal raphe, MAO-A and MAO-B expressions were determined with in situ hybridization (ISH) and protein expression of aromatase was determined with immunohistochemistry (IHC). CSF concentrations of 5HIAA, 3-methoxy-4-hydroxyphenylglycol (MHPG), and homovanillic acid (HVA) were determined with liquid chromatography/mass spectrometry (LC/MS). From the same animals, previously published data on serotonin axon density were used as a proxy for CNS serotonin. Aromatase conversion of T to estrogen (E) suppressed MAO-A (positive pixel area, p=0.0045), but androgens increased MAO-B (positive pixel area, p=0.014). CSF 5HIAA was suppressed by conversion of T to E (Cohen's d=0.6). CSF 5HIAA was positively correlated with MAO-A-positive pixel area (r2=0.78). CSF 5HIAA was inversely correlated with serotonin axon-positive pixel area (r2=0.69). In summary, CSF 5HIAA reflects MAO-A activity rather than global serotonin. Low CSF 5HIAA may, in this paradigm, reflect higher serotonin activity. Androgens lower MAO-A activity via metabolism to E, thus elevating CNS serotonin and decreasing CSF 5HIAA. Since androgens increase certain types of aggression, these data are consistent with studies demonstrating that lower MAO-A activity is associated with elevated serotonin and increased aggression.

Bhat, S. R., Meng, N. F., Kumar, K., Nagesh, K. N., Kawale, A., & Bhutani, V. K. (2015). Keeping babies warm: A non-inferiority trial of a conductive thermal mattress. *Archives of Disease in Childhood: Fetal and Neonatal Edition*,

Background External thermal support is critical for preterm or ill infants due to altered thermoregulation. Incubators are the gold standard for long-term support and have been adopted successfully in many countries. Alternatives such as radiant warmers, blankets and others are often used as standard of care (SoC) in resource-limited settings when infants are otherwise not

in Kangaroo Mother Care (KMC). Methods In this pilot study, we evaluate the feasibility of a conductive thermal mattress (CTM) using phase change materials as a low-cost warmer. We conducted a prospective multicentre open-label randomised controlled trial to determine non-inferiority of this CTM to SoC warming practices in low birthweight infants. The primary outcome was maintenance of axillary temperature. Results We equally randomised 160 infants to CTM or SoC. The latter cohort continued to receive warmth by radiant warmers (n=48), blankets (n=18), warmed cradles (n=7) or KMC (n=7) before, during and subsequent to the study. CTM was deemed non-inferior since warmed babies had higher axillary temperature compared with SoC (mean increase 0.11±0.03°C SEM; p<0.001). Post hoc comparison to radiant warmers alone showed that CTM led to a higher axillary temperature (mean increase by 0.14±0.03°C SEM; p<0.001). Conclusions Short-term use of CTM compared with radiant warmers and other modes of warming is non-inferior to SoC and efficacious in maintaining body temperature. No adverse effects were reported. An extended multinational trial, preferably one that demonstrates longer-term thermoregulation, is warranted.

Bittel, A. M., Saldivar, I., Dolman, N., Nickerson, A. K., Lin, L. -., Nan, X., et al. (2015). Effect of labeling density and time post labeling on quality of antibody-based super resolution microscopy images. *Single Molecule Spectroscopy and Superresolution Imaging VIII*, , *9331.*

Super resolution microscopy (SRM) has overcome the historic spatial resolution limit of light microscopy, enabling fluorescence visualization of intracellular structures and multi-protein complexes at the nanometer scale. Using single-molecule localization microscopy, the precise location of a stochastically activated population of photoswitchable fluorophores is determined during the collection of many images to form a single image with resolution of ~10-20 nm, an order of magnitude improvement over conventional microscopy. One of the key factors in achieving such resolution with single-molecule SRM is the ability to accurately locate each fluorophore while it emits photons. Image quality is also related to appropriate labeling density of the entity of interest within the sample. While ease of detection improves as entities are labeled with more fluorophores and have increased fluorescence signal, there is potential to reduce localization precision, and hence resolution, with an increased number of fluorophores that are on

at the same time in the same relative vicinity. In the current work, fixed microtubules were antibody labeled using secondary antibodies prepared with a range of Alexa Fluor 647 conjugation ratios to compare image quality of microtubules to the fluorophore labeling density. It was found that image quality changed with both the fluorophore labeling density and time between completion of labeling and performance of imaging study, with certain fluorophore to protein ratios giving optimal imaging results. © 2015 SPIE.

Bleyer, A. (2015). Screening mammography: Update and review of publications since our report in the new england journal of medicine on the magnitude of the problem in the united states. *Academic Radiology*,

RATIONALE AND OBJECTIVES: After a half century of clinical trials, expansive observations, vigorous advocacy and debate, screening mammography could not be in a more controversial condition, especially the potential harm of overdiagnosis. Despite a simple rationale (catch the cancer early and either prevent death or at least decrease the amount of therapy needed for cure), the estimates to date of overdiagnosis rates are conflicting and the interpretations complex. MATERIALS AND METHODS: Since the author's 2012 publication in the New England Journal of Medicine (NEJM), the peer-reviewed publications on overdiagnosis caused by screening mammography are reviewed and the NEJM analyses updated with three additional calendar years of results. RESULTS: The recent peer-reviewed medical literature on screening mammography induced overdiagnosis of breast cancer has increased exponentially, nearly 10-fold in 10 years. The average estimate of overdiagnosis is about 30%, but the range extends from 0% to 70+%. An update of the NEJM report estimates that in the US, 78,000 women and 30%-31% of those diagnosed with breast cancer at the age of 40 years or older during 2011 were overdiagnosed. CONCLUSIONS: Until we have better screening procedures that identify who really has cancer and needs to be treated, the risk of overdiagnosis relative to the benefit of screening merits more effective public and professional education. Radiologists, pathologists, and other professionals involved with screening mammography should recognize that the potential harm of overdiagnosis is downplayed or not discussed with the patient and family, despite agreement that the objective is informed choice.

Bloom, J. D. (2015). Psychiatric boarding in washington state and the inadequacy of mental health resources. *The Journal of the American Academy of Psychiatry and the Law, 43*(2), 218-222.

Psychiatric boarding is a term derived from emergency medicine that describes the holding of patients deemed in need of hospitalization in emergency departments for extended periods because psychiatric beds are not available. Such boarding has occurred for many years in the shadows of mental health care as both inpatient beds and community services have decreased. This article focuses on a 2014 Washington State Supreme Court decision that examined the interpretation of certain sections of the Washington state civil commitment statute that had been used to justify the extended boarding of detained psychiatric patients in general hospital emergency departments. The impact of this decision on the state of Washington should be significant and could spark a national debate about the negative impacts of psychiatric boarding on patients and on the nation's general hospital emergency services.

Boone-Heinonen, J., Howard, A. G., Meyer, K., Lewis, C. E., Kiefe, C. I., Laroche, H. H., et al. (2015). Marriage and parenthood in relation to obesogenic neighborhood trajectories: The CARDIA study. *Health & Place, 34*, 229-240.

Marriage and parenthood are associated with weight gain and residential mobility. Little is known about how obesity-relevant environmental contexts differ according to family structure. We estimated trajectories of neighborhood poverty, population density, and density of fast food restaurants, supermarkets, and commercial and public physical activity facilities for adults from a biracial cohort (CARDIA, n=4,174, aged 25-50) over 13 years (1992-93 through 2005-06) using latent growth curve analysis. We estimated associations of marriage, parenthood, and race with the observed neighborhood trajectories. Married participants tended to live in neighborhoods with lower poverty, population density, and availability of all types of food and physical activity amenities. Parenthood was similarly but less consistently related to neighborhood characteristics. Marriage and parenthood were more strongly related to neighborhood trajectories in whites (versus blacks), who, in prior studies, exhibit weaker associations between neighborhood characteristics and health. Greater understanding of how interactive family and neighborhood environments contribute to healthy living is needed.

Botto, S., Totonchy, J. E., Gustin, J. K., & Moses, A. V. (2015). Kaposi sarcoma herpesvirus induces HO-1 during de novo infection of endothelial cells via viral miRNA-dependent and -independent mechanisms. *Mbio, 6*(3), 10.1128/mBio.00668-15.

Kaposi sarcoma (KS) herpesvirus (KSHV) infection of endothelial cells (EC) is associated with strong induction of heme oxygenase-1 (HO-1), a stress-inducible host gene that encodes the rate-limiting enzyme responsible for heme catabolism. KS is an angioproliferative tumor characterized by the proliferation of KSHV-infected spindle cells, and HO-1 is highly expressed in such cells. HO-1 converts the pro-oxidant, proinflammatory heme molecule into metabolites with antioxidant, anti-inflammatory, and proliferative activities. Previously published work has shown that KSHV-infected EC in vitro proliferate in response to free heme in a HO-1-dependent manner, thus implicating virus-enhanced HO-1 activity in KS tumorigenesis. The present study investigated the molecular mechanisms underlying KSHV induction of HO-1 in lymphatic EC (LEC), which are the likely spindle cell precursors. In a time course analysis of KSHV-infected cells, HO-1 expression displays biphasic kinetics characterized by an early transient induction that is followed by a more sustained upregulation coincident with the establishment of viral latency. A viral microRNA miR-K12-11 deletion mutant of KSHV was found to be defective for induction of HO-1 during latency. A potential mechanism for this phenotype was provided by BACH1, a cellular HO-1 transcriptional repressor targeted by miR-K12-11. In fact, in KSHV-infected LEC, the BACH1 message level is reduced, BACH1 subcellular localization is altered, and miR-K12-11 mediates the inverse regulation of HO-1 and BACH1 during viral latency. Interestingly, the data indicate that neither miR-K12-11 nor de novo KSHV gene expression is required for the burst of HO-1 expression observed at early times postinfection, which suggests that additional virion components promote this phenotype. IMPORTANCE: While the mechanisms underlying KSHV induction of HO-1 remain unknown, the cellular mechanisms that regulate HO-1 expression have been extensively investigated in the context of basal and pathophysiological states. The detoxifying action of HO-1 is critical for the protection of cells exposed to high heme levels. KS spindle cells are erythrophagocytic and contain erythrocyte ghosts. Erythrocyte degeneration leads to the localized release of heme, creating oxidative stress that may be further exacerbated by environmental or other cofactors. Our previous work showed that KSHV-infected cells proliferate in response to heme and that this occurs in a HO-1-dependent manner. We therefore

hypothesize that KSHV induction of HO-1 contributes to KS tumor development via heme metabolism and propose that HO-1 be evaluated as a therapeutic target for KS. Our present work, which aimed to understand the mechanisms whereby KSHV induces HO-1, will be important for the design and implementation of such a strategy.

Campens, L., Renard, M., Trachet, B., Segers, P., Muino Mosquera, L., De Sutter, J., et al. (2015). Intrinsic cardiomyopathy in marfan syndrome: Results from in- and ex-vivo studies of the Fbn1 model and longitudinal findings in humans. *Pediatric Research*,

BACKGROUND: Mild intrinsic cardiomyopathy in patients with Marfan syndrome (MFS) has consistently been evidenced by independent research groups. So far, little is known about the long-term evolution and pathophysiology of this finding. METHODS: To gain more insights into the pathophysiology of MFS-related cardiomyopathy, we performed in- and ex-vivo studies of 11 Fbn1C1039G/+ mice and 9 WT littermates. Serial ultrasound findings obtained in mice were correlated to the human phenotype. We therefore re-assessed LV function parameters over a 6 year follow-up period in 19 previously reported MFS patients, in whom we documented mild LV dysfunction. RESULTS: Fbn1C1039G/+ mice demonstrated LV contractile dysfunction. Subsequent ex-vivo studies of the myocardium of adult mutant mice revealed upregulation of TGFbeta-related pathways and consistent abnormalities of the microfibrillar network, implicating a role for microfibrils in the mechanical properties of the myocardium. Echocardiographic parameters did not indicate clinical significant deterioration of LV function during follow-up in our patient cohort. CONCLUSION: In analogy with what is observed in the majority of MFS patients, the Fbn1C1039G/+ mouse model demonstrates mild intrinsic LV dysfunction. Both extracellular matrix and molecular alterations are implicated in MFS-related cardiomyopathy. This model may now enable us to study therapeutic interventions on the myocardium in MFS.Pediatric Research (2015); doi:10.1038/pr.2015.110.

Campian, J. L., Ye, X., Gladstone, D. E., Ambady, P., Nirschl, T. R., Borrello, I., et al. (2015). Pre-radiation lymphocyte harvesting and post-radiation reinfusion in patients with newly diagnosed high grade gliomas. *Journal of Neuro-Oncology*,

Radiation (RT), temozolomide (TMZ), and dexamethasone in newly diagnosed high grade gliomas

(HGG) produces severe treatment-related lymphopenia (TRL) that is associated with early cancer-related deaths. This TRL may result from inadvertent radiation to circulating lymphocytes. This study reinfused lymphocytes, harvested before chemo-radiation, and assessed safety, feasibility, and trends in lymphocyte counts. Patients with newly diagnosed HGG and total lymphocyte counts (TLC) ≥ 1000 cells/mm3 underwent apheresis. Cryopreserved autologous lymphocytes were reinfused once radiation was completed. Safety, feasibility, and trends in TLC, T cell subsets and cytokines were studied. Serial TLC were also compared with an unreinfused matched control group. Ten patients were harvested (median values: age 56 years, dexamethasone 3 mg/day, TLC/CD4 1980/772 cells/mm3). After 6 weeks of RT/TMZ, TLC fell 69 % ($p < 0.0001$) with similar reductions in CD4, CD8 and NK cells but not Tregs. Eight patients received lymphocyte reinfusions (median = 7.0 × 107 lymphocytes/kg) without adverse events. A post-reinfusion TLC rise of ≥300 cells/mm3 was noted in 3/8 patients at 4 weeks and 7/8 at 14 weeks which was similar to 23 matched controls. The reduced CD4/CD8 ratio was not restored by lymphocyte reinfusion. Severe lymphopenia was not accompanied by elevated serum interleukin-7 (IL-7) levels. This study confirms that severe TRL is common in HGG and is not associated with high plasma IL-7 levels. Although lymphocyte harvesting/reinfusion is feasible and safe, serial lymphocyte counts are similar to unreinfused matched controls. Studies administering higher lymphocyte doses and/or IL-7 should be considered to restore severe treatment-related lymphopenia in HGG.

Cannady, S. B., Lamarre, E., & Wax, M. K. (2015). Microvascular reconstruction. evidence-based procedures. *Facial Plastic Surgery Clinics of North America*,

Microvascular free tissue transfer is the best modality of replacing composite tissue defects with composite vascularized tissue. Wound healing, functional reconstruction, rehabilitation, and cosmesis are best accomplished when the tissue defect is replaced by free tissue. The reconstructive tissue can be tailored to the defect and is harvested from outside the often radiated pretreated reconstructive field. Evidence to support the use of free tissue transfer in head and neck defects is not of the highest level. This article reviews the postoperative monitoring of free tissue transfer, lateral mandibular reconstruction (fibula vs radial forearm), and functional outcomes with free tissue transfers.

Casey, C. M., Salinas, K., & Eckstrom, E. (2015). Electronic health record tools to care for at-risk older drivers: A quality improvement project. *The Gerontologist, 55 Suppl 1*, S128-39.

PURPOSE OF THE STUDY: Evaluating driving safety of older adults is an important health topic, but primary care providers (PCP) face multiple barriers in addressing this issue. The study's objectives were to develop an electronic health record (EHR)-based Driving Clinical Support Tool, train PCPs to perform driving assessments utilizing the tool, and systematize documentation of assessment and management of driving safety issues via the tool. DESIGN AND METHODS: The intervention included development of an evidence-based Driving Clinical Support Tool within the EHR, followed by training of internal medicine providers in the tool's content and use. Pre- and postintervention provider surveys and chart review of driving-related patient visits were conducted. Surveys included self-report of preparedness and knowledge to evaluate at-risk older drivers and were analyzed using paired t-test. A chart review of driving-related office visits compared documentation pre- and postintervention including: completeness of appropriate focused history and exam, identification of deficits, patient education, and reporting to appropriate authorities when indicated. RESULTS: Data from 86 providers were analyzed. Pre- and postintervention surveys showed significantly increased self-assessed preparedness ($p < .001$) and increased driving-related knowledge ($p < .001$). Postintervention charts showed improved documentation of correct cognitive testing, more referrals/consults, increased patient education about community resources, and appropriate regulatory reporting when deficits were identified. IMPLICATIONS: Focused training and an EHR-based clinical support tool improved provider self-reported preparedness and knowledge of how to evaluate at-risk older drivers. The tool improved documentation of driving-related issues and led to improved access to interdisciplinary care coordination.

Castle, J. R. (2015). Is glucagon needed in type 1 diabetes? *The Lancet.Diabetes & Endocrinology*,

Caughey, A. B. (2015). The editorialist replies. *New England Journal of Medicine, 372*(23), 2267-2268.

Caughey, A. B. (2015). Increasing rates of induction do not increase caesareans. *BJOG: An International Journal of Obstetrics and Gynaecology, 122*(7), 981.

Caverzagie, K. J., Cooney, T. G., Hemmer, P. A., & Berkowitz, L. (2015). The development of entrustable professional activities for internal medicine residency training: A report from the education redesign committee of the alliance for academic internal medicine. *Academic Medicine : Journal of the Association of American Medical Colleges*, *90*(4), 479-484.

PURPOSE: The Alliance for Academic Internal Medicine charged its Education Redesign Committee with the task of assisting internal medicine residency program directors in meeting the challenges of competency-based assessment that were part of the Accreditation Council for Graduate Medical Education's (ACGME's) Next Accreditation System. METHOD: Recognizing the limitations of the ACGME general competencies as an organizing framework for assessment and the inability of the milestones to provide the needed context for faculty to assess residents' competence, the Education Redesign Committee in 2011 adopted the work-based assessment framework of entrustable professional activities (EPAs). The committee selected the EPA framework after reviewing the literature on competency-based education and EPAs and consulting with experts in evaluation and assessment. The committee used an iterative approach with broad-based feedback from multiple sources, including program directors, training institutions, medical organizations, and specialty societies, to develop a set of EPAs that together define the core of the internal medicine profession. RESULTS: The resulting 16 EPAs are those activities expected of a resident who is ready to enter unsupervised practice, and they provide a starting point from which training programs could develop assessments and curricula. The committee also provided a strategy for the use of these EPAs in competency-based evaluation. CONCLUSIONS: These EPAs are intended to serve as a starting point or guide for program directors to begin developing meaningful, work-based assessments that inform the evaluation of residents' competence.

Centeno, C., Pitts, J., Al-Sayegh, H., & Freeman, M. (2014). Efficacy of autologous bone marrow concentrate for knee osteoarthritis with and without adipose graft. *BioMed Research International*, *2014*, 370621.

INTRODUCTION: We investigated the use of autologous bone marrow concentrate (BMC) with and without an adipose graft, for treatment of knee osteoarthritis (OA). METHODS: Treatment registry data for patients who underwent BMC procedures with and without an adipose graft were analyzed. Pre- and posttreatment outcomes of interest included the lower extremity functional

scale (LEFS), the numerical pain scale (NPS), and a subjective percentage improvement rating. Multivariate analyses were performed to examine the effects of treatment type adjusting for potential confounding factors. The frequency and type of adverse events (AE) were also examined. RESULTS: 840 procedures were performed, 616 without and 224 with adipose graft. The mean LEFS score increased by 7.9 and 9.8 in the two groups (out of 80), respectively, and the mean NPS score decreased from 4 to 2.6 and from 4.3 to 3 in the two groups, respectively. AE rates were 6% and 8.9% in the two groups, respectively. Although pre- and posttreatment improvements were statistically significant, the differences between the groups were not. CONCLUSION: BMC injections for knee OA showed encouraging outcomes and a low rate of AEs. Addition of an adipose graft to the BMC did not provide a detectible benefit over BMC alone.

Centeno, C. J., Al-Sayegh, H., Bashir, J., Goodyear, S., & Freeman, M. D. (2015). A prospective multi-site registry study of a specific protocol of autologous bone marrow concentrate for the treatment of shoulder rotator cuff tears and osteoarthritis. *Journal of Pain Research, 8*, 269-276. INTRODUCTION: Shoulder pain is a common musculoskeletal complaint in the general population. Bone marrow concentrate (BMC) injections offer promising potential as a minimally invasive approach for treatment of shoulder pain in degenerative disease. In this study, we investigated the clinical outcomes of the BMC injections for treatment of shoulder pain and disability due to osteoarthritis (OA) and rotator cuff tears in a treatment registry population. METHODS: A total of 115 shoulders in 102 patients were treated with autologous BMC injections for symptomatic OA at the glenohumeral joint and/or rotator cuff tears. Data were collected for factors potentially influencing outcome, including age, sex, body mass index, and the type of condition treated (ie, OA or rotator cuff tear). Clinical outcomes were assessed serially over time using the disabilities of the arm, shoulder and hand score (DASH), the numeric pain scale (NPS), and a subjective improvement rating scale. Baseline scores were compared to the most recent outcome scores at the time of the analysis and adjusted for demographic differences. We reported comparisons of pre- and post-treatment scores, the differences between osteoarthritis and rotator cuff groups, and the predictive effects on the clinical outcomes. RESULTS: At the most current follow-up assessment after treatment, the average DASH score decreased (improved) from 36.1 to 17.1 ($P<0.001$) and the average numeric pain scale value decreased (improved) from 4.3 to 2.4

(P<0.001). These changes were associated with an average subjective improvement of 48.8%. No differences were observed between outcomes among the shoulders treated for OA versus rotator cuff tears, nor did age, sex, or body mass index influence pain or functional outcomes. There were no significant treatment-related adverse events reported. DISCUSSION: We observed preliminarily encouraging results following BMC injections for shoulder OA and rotator cuff tears. These results serve as basis for the design of an adequately powered randomized controlled trial.

Chamberlain, E., DiVeronica, M., & Segura, R. (2015). When medical care leads to harm-difficulty finding words: A teachable moment. *JAMA Internal Medicine*,

Chapman, B. K., Davulcu, O., Skalicky, J. J., Bruschweiler, R. P., & Chapman, M. S. (2015). Parsimony in protein conformational change. *Structure (London, England : 1993)*,

Protein conformational change is analyzed by finding the minimalist backbone torsion angle rotations that superpose crystal structures within experimental error. Of several approaches for enforcing parsimony during flexible least-squares superposition, an l1-norm restraint provided greatest consistency with independent indications of flexibility from nuclear magnetic resonance relaxation dispersion and chemical shift perturbation in arginine kinase and four previously studied systems. Crystallographic cross-validation shows that the dihedral parameterization describes conformational change more accurately than rigid-group approaches. The rotations that superpose the principal elements of structure constitute a small fraction of the raw (phi, psi) differences that also reflect local conformation and experimental error. Substantial long-range displacements can be mediated by modest dihedral rotations, accommodated even within alpha helices and beta sheets without disruption of hydrogen bonding at the hinges. Consistency between ligand-associated and intrinsic motions (in the unliganded state) implies that induced changes tend to follow low-barrier paths between conformational sub-states that are in intrinsic dynamic equilibrium.

Choi, C. E., Sonnenberg, A., Turner, K., & Genta, R. M. (2015). High prevalence of gastric preneoplastic lesions in east asians and hispanics in the USA. *Digestive Diseases and Sciences, 60*(7), 2070-2076.

Background: The prevalence of H. pylori infection and the incidence of gastric cancer differ widely

around the world, but it is unclear whether these differences are mirrored in the multiethnic population of the USA. Aims: This study tested the hypothesis that the prevalence of both H. pylori infection and gastric preneoplastic lesions in US residents of Hispanic and Asian ancestry reflects the incidence of gastric cancer in their ancestral countries. Methods: A total of 799,075 subjects with gastric biopsies extracted from a national pathology database were stratified into the following ancestries: Indian, Hispanic, Vietnamese, Chinese, Japanese Korean, and other Americans (Caucasian and African-American US residents). The prevalence of H. pylori, intestinal metaplasia, and atrophic gastritis was compared among different ethnic groups using age- and sex-adjusted odds ratios and linear regression. Results: Patients of Indian, Hispanic, Vietnamese, Chinese, Japanese, and Korean ancestry had significantly higher prevalence rates of H. pylori gastritis, intestinal metaplasia, and atrophy than other Americans. The prevalence of intestinal metaplasia and atrophy among different ethnic groups did not correlate with H. pylori prevalence, but did correlate highly significantly with gastric cancer incidence in the patients' ancestral countries. Conclusions: Various US ethnic groups have significantly different prevalence rates of H. pylori gastritis and gastric preneoplastic lesions. Patients' ethnicity needs be considered in the prevention and early detection of gastric cancer. © 2015, Springer Science+Business Media New York.

Choi, Y. S., Kim, D. H., Park, J. H., Johnstone, B., & Yoo, J. U. (2015). Effectiveness of posterolateral lumbar fusion varies with the physical properties of demineralized bone matrix strip. *Asian Spine Journal*, *9*(3), 433-439.

STUDY DESIGN: A randomized, controlled animal study. PURPOSE: To investigate the effectiveness of fusion and new bone formation induced by demineralized bone matrix (DBM) strips with jelly strengths. OVERVIEW OF LITERATURE: The form of the DBM can make a difference to the outcome. The effect of different jelly strengths on the ability of DBM to form new bone is not known. METHODS: Forty-eight rabbits were randomized into a control group and two experimental groups. In the control group (group 1), 1.4 g of autologous iliac crest bone was placed bilaterally. In the experimental groups, a high jelly strength DBM-hyaluronic acid (HA)-gelatin strip (group 2) and a low jelly strength DBM-HA-gelatin strip (group 3) were used. The fusion was assessed with manual manipulation and radiographs. The volume of the fusion mass

was determined from computed tomographic images. RESULTS: The fusion rates as determined by manual palpation were 37.5%, 93.8% and 50.0% in group 1, group 2, and group 3, respectively ($p<0.05$). By radiography, the fusion rate of High jelly strength DBM strip was statistically significantly greater than that of the other alternatives ($p<0.05$). The mean bone volume of the fusion mass as determined by computed tomography was 2,142.2+/-318.5 mm(3), 3,132.9+/-632.1 mm(3), and 2,741.5+/-380.4 mm(3) in group 1, group 2, and group 3, respectively ($p<0.05$). CONCLUSIONS: These results indicate that differences in the structural and mechanical properties of gelatin that are associated with jelly strength influenced cellular responses such as cell viability and bony tissue ingrowth, facilitating greater bone fusion around high jelly strength implants.

Chornokur, G., Lin, H. Y., Tyrer, J. P., Lawrenson, K., Dennis, J., Amankwah, E. K., et al. (2015). Common genetic variation in cellular transport genes and epithelial ovarian cancer (EOC) risk. *PloS One*, *10*(6), e0128106.

BACKGROUND: Defective cellular transport processes can lead to aberrant accumulation of trace elements, iron, small molecules and hormones in the cell, which in turn may promote the formation of reactive oxygen species, promoting DNA damage and aberrant expression of key regulatory cancer genes. As DNA damage and uncontrolled proliferation are hallmarks of cancer, including epithelial ovarian cancer (EOC), we hypothesized that inherited variation in the cellular transport genes contributes to EOC risk. METHODS: In total, DNA samples were obtained from 14,525 case subjects with invasive EOC and from 23,447 controls from 43 sites in the Ovarian Cancer Association Consortium (OCAC). Two hundred seventy nine SNPs, representing 131 genes, were genotyped using an Illumina Infinium iSelect BeadChip as part of the Collaborative Oncological Gene-environment Study (COGS). SNP analyses were conducted using unconditional logistic regression under a log-additive model, and the FDR $q<0.2$ was applied to adjust for multiple comparisons. RESULTS: The most significant evidence of an association for all invasive cancers combined and for the serous subtype was observed for SNP rs17216603 in the iron transporter gene HEPH (invasive: OR = 0.85, P = 0.00026; serous: OR = 0.81, P = 0.00020); this SNP was also associated with the borderline/low malignant potential (LMP) tumors (P = 0.021). Other genes significantly associated with EOC histological subtypes ($p<0.05$) included the

UGT1A (endometrioid), SLC25A45 (mucinous), SLC39A11 (low malignant potential), and SERPINA7 (clear cell carcinoma). In addition, 1785 SNPs in six genes (HEPH, MGST1, SERPINA, SLC25A45, SLC39A11 and UGT1A) were imputed from the 1000 Genomes Project and examined for association with INV EOC in white-European subjects. The most significant imputed SNP was rs117729793 in SLC39A11 (per allele, OR = 2.55, 95% CI = 1.5-4.35, p = 5.66x10-4). CONCLUSION: These results, generated on a large cohort of women, revealed associations between inherited cellular transport gene variants and risk of EOC histologic subtypes.

Chou, R. (2014). In response. *Annals of Internal Medicine*, *161*(10), 762.

Chou, S. (2015). Approach to drug-resistant cytomegalovirus in transplant recipients. *Current Opinion in Infectious Diseases*, *28*(4), 293-299.

PURPOSE OF REVIEW: The purpose of this study is to provide updated information on diagnosis of cytomegalovirus (CMV) drug resistance, treatments for drug-resistant infection and potential uses of experimental antiviral compounds. RECENT FINDINGS: For established CMV antivirals, uncommon viral UL97 kinase and UL54 DNA polymerase drug resistance mutations are sporadically described that expand an extensive existing database. Some novel mutations reported from treated patients have no drug-resistant phenotype and may be genotyping artefacts. Next-generation sequencing technology may enable earlier detection of emerging resistance mutations in treated patients. Management options for drug-resistant infection include optimization of host defenses, antiviral dose escalation, substitutions or combinations of standard or experimental antivirals. Maribavir and letermovir have antiviral targets distinct from the classic DNA polymerase. UL97 mutations elicited by ganciclovir and maribavir are different, although a single p-loop mutation can confer significant cross-resistance. High-grade resistance mutations in the UL56 terminase gene are readily selected in vitro under letermovir and await clinical correlation. SUMMARY: Technical advancements can enhance the accurate and timely genotypic detection of drug resistance. Antivirals undergoing clinical trial offer the prospect of new viral targets and drug combinations, but unresolved issues exist with regard to their therapeutic potential for drug-resistant CMV and their genetic barriers to resistance.

Colangelo, L. A., Vu, T. H., Szklo, M., Burke, G. L., Sibley, C., & Liu, K. (2015). Is the association of hypertension with cardiovascular events stronger among the lean and normal weight than among the overweight and obese? the multi-ethnic study of atherosclerosis. *Hypertension*,

Previous studies that suggest the association of hypertension with cardiovascular disease (CVD) events is stronger in the lean/normal weight than in the obese have either included smokers, diabetics, or cancer patients, or did not account for central obesity. This study examines the interaction of adiposity with hypertension on CVD events using body mass index (BMI)-based definitions of overweight and obesity, as well as waist circumference (WC) to assess adiposity. In the Multi-Ethnic Study of Atherosclerosis, we classified 3657 nonsmoking men and women, free of baseline clinical CVD, diabetes mellitus and cancer, into 7 BMI-WC combinations defined by ethnicity-specific BMI (normal, overweight, class 1 obese, and class 2/3 obese) and ethnicity- and sex-specific WC categories (optimal or nonoptimal). Adjusted absolute event rates per 1000 person-years and relative risks (95% confidence intervals) for CVD events for hypertension (blood pressure >/=140/90 or taking medication) versus no hypertension computed within adiposity categories were 9.3 versus 1.9 and 4.96 (2.56-9.60) for normal BMI/optimal WC, 13.2 versus 4.2 and 3.13 (0.99-9.86) for normal BMI/nonoptimal WC, 9.0 versus 4.5 and 2.00 (1.19-3.36) for overweight BMI/optimal WC, 8.4 versus 5.6 and 1.50 (0.88-2.54) for overweight BMI/nonoptimal WC,14.1 versus 2.1 and 6.75 (0.69-65.57) for class 1 obese/optimal WC, 10.1 versus 3.7 and 2.69 (1.41-5.16) for class 1 obese/nonoptimal WC, and 9.9 versus 6.9 and 1.45(0.60-3.52) for class 2/3 obese/WC pooled. This study found a large relative risk of CVD events associated with hypertension for normal BMI participants and more importantly similarly high absolute risks for both normal and obese BMI with hypertension.

Collin, P., Treseder, T., Denard, P. J., Neyton, L., Walch, G., & Lädermann, A. (2015). What is the best clinical test for assessment of the teres minor in massive rotator cuff tears? *Clinical Orthopaedics and Related Research*,

Background: Few studies define the clinical signs to evaluate the integrity of teres minor in patients with massive rotator cuff tears. CT and MRI, with or without an arthrogram, can be limited by image quality, soft tissue density, motion artifact, and interobserver reliability. Additionally, the ill-defined junction between the infraspinatus and teres minor and the larger

muscle-to-tendon ratio of the teres minor can contribute to error. Therefore, we wished to determine the validity of clinical testing for teres minor tears. Question/Purposes: The aim of this study was to determine the accuracy of commonly used clinical signs (external rotation lag sign, drop sign, and the Patte test) for diagnosing the teres minor's integrity. Methods: We performed a prospective evaluation of patients referred to our shoulder clinic for massive rotator cuff tears determined by CT arthrograms. The posterosuperior rotator cuff was examined clinically and correlated with CT arthrograms. We assessed interobserver reliability for CT assessment and used three different clinical tests of teres minor function (the external rotation lag sign, drop sign, and the Patte test). One hundred patients with a mean age of 68 years were available for the analysis. Results: The most accurate test for teres minor dysfunction was an external rotation lag sign greater than 40°, which had a sensitivity of 100% (95% CI, 80%–100%) and a specificity of 92% (95% CI, 84%–96%). External rotation lag signs greater than 10° had a sensitivity of 100% (95% CI, 80%–100%) and a specificity of 51% (95% CI, 40%–61%). The Patte sign had a sensitivity of 93% (95% CI, 70%–99%) and a specificity of 72% (95% CI, 61%–80%). The drop sign had a sensitivity of 87% (95% CI, 62%–96%) and a specificity of 88% (95% CI, 80%–93%). An external rotation lag sign greater than 40° was more specific than an external rotation lag sign greater than 10° ($p < 0.001$), and a Patte sign ($p < 0.001$), but was not more specific than the drop sign ($p < 0.47$). There was poor correlation between involvement of the teres minor and loss of active external rotation. Conclusions: Clinical signs can predict anatomic patterns of teres minor dysfunction with good accuracy in patients with massive rotator cuff tears. This study showed that the most accurate test for teres minor dysfunction is an external rotation lag sign and that most patients' posterior rotator cuff tears do not lose active external rotation. Because imaging is not always accurate, examination for integrity of the teres minor is important because it may be one of the most important variables affecting the outcome of reverse shoulder arthroplasty for massive rotator cuff tears, and the functional effects of tears in this muscle on day to day activities can be significant. Additionally, teres minor integrity affects the outcomes of tendon transfers, therefore knowledge of its condition is important in planning repairs. Level of Evidence: Level III, diagnostic study.

Collins, L. C., Gelber, S., Marotti, J. D., White, S., Ruddy, K., Brachtel, E. F., et al. (2015). Molecular phenotype of breast cancer according to time since last pregnancy in a large cohort of young women. *The Oncologist*,

BACKGROUND: The increase in breast cancer risk during pregnancy and postpartum is well known; however, the molecular phenotype of breast cancers occurring shortly after pregnancy has not been well studied. Given this, we investigated whether nulliparity and the time interval since pregnancy among parous women affects the breast cancer phenotype in young women. MATERIALS AND METHODS: We examined molecular phenotype in relation to time since pregnancy in a prospective cohort of 707 young women (aged 5 years after pregnancy had more luminal A-like subtypes than women with shorter intervals since pregnancy, there was no evidence of a relationship between these intervals and molecular subtypes once family history of breast cancer and age at diagnosis were considered. CONCLUSION: Distribution of breast cancer molecular phenotype did not differ significantly among young women by parity or time interval since parturition when important predictors of tumor phenotype such as age and family history were considered.

Coombs, P. G., Feldman, B. H., Lauer, A. K., Paul Chan, R. V., & Sun, G. (2015). Global health training in ophthalmology residency programs. *Journal of Surgical Education*, *72*(4), e52-9.

PURPOSE: To assess current global health education and international electives in ophthalmology residency programs and barriers to global health implementation in ophthalmology resident education. METHODS: A web-based survey regarding participation in global health and international electives was emailed to residency program directors at 116 accredited ophthalmology residency programs via an Association of University Professors in Ophthalmology (AUPO) residency program director listserv. RESULTS: Fifty-nine (51%) ophthalmology residency program directors responded. Thirty-seven program directors (63%) said global health was important to medical students when evaluating residency programs. Thirty-two program directors (55%) reported developing international electives. Reported barriers to resident participation in international electives were: 1) insufficient financial support, 2) inadequate resident coverage at home, and 3) lack of ACGME approval for international electives. Program directors requested more information about resident international electives, funding, and global ophthalmology

educational resources. They requested ACGME recognition of international electives to facilitate resident participation. More than half (54%) of program directors supported international electives for residents. CONCLUSIONS: This survey demonstrates that program directors believe global health is an important consideration when medical students evaluate training programs. Despite perceived barriers to incorporating global health opportunities into residency training, program directors are interested in development of global health resources and plan to further develop global health opportunities.

Cowan, N. G., Banerji, J. S., Johnston, R. B., Duty, B. D., Bakken, B., Hedges, J. C., et al. (2015). Renal autotransplantation: 27-year experience at two institutions. *The Journal of Urology*, PURPOSE: Renal autotransplantation is an infrequently performed procedure. It has been used for the management of complex ureteral disease, vascular anomalies, and chronic kidney pain. Herein is reviewed our 27-year experience with this procedure. MATERIALS AND METHODS: This is a retrospective observational study of 51 consecutive patients who underwent renal autotransplantation at the Oregon Health and Science University(N=29 between 1986-2013) and Virginia Mason(N=22 between 2007-2012). Demographics, indications, operative details, and follow up data were collected. Early(30 days) complications were graded according to the Clavien-Dindo system. Factors associated with complications and pain recurrence were evaluated using a logistic regression model. RESULTS: 51 patients underwent 54 renal autotransplants. The median follow up was 21.5 months. The most common indications were loin pain hematuria syndrome(LPHS)/chronic kidney pain(31.5%), ureteral stricture(20.4%), and vascular anomalies(18.5%). Autotransplantation of a solitary kidney was performed in 5 patients. Laparoscopic nephrectomy was performed in 23.5% of cases. Median operative time was 402 minutes and the median length of stay was 6 days. No significant difference was found between preoperative and postoperative plasma creatinine (p=0.74). Early high-grade complications(>/=Grade III-a) occurred in 14.8% of patients and 12.9% of patients experienced late complications of any grade. Two graft losses occurred. Longer cold ischemia time was associated with complications(p=0.049). 35% of patients who underwent autotransplantation for chronic kidney pain had a recurrence, and 2 patients underwent transplant nephrectomy. No predictors of pain recurrence were identified. CONCLUSIONS: The most common indications for

renal autotransplantation were LPHS/chronic kidney pain, ureteral stricture, and vascular anomalies, respectively. Kidney function was preserved post-operatively and two graft losses occurred. 65% of patients who underwent the procedure for pain had resolution of the pain at a median follow up of 13 months. Complication rates compared favorably with other major urologic operations and cold ischemia time was the only predictor of postoperative complications.

Crowell, T. A., Gebo, K. A., Blankson, J. N., Korthuis, P. T., Yehia, B. R., Rutstein, R. M., et al. (2015). Hospitalization rates and reasons among HIV elite controllers and persons with medically controlled HIV infection. *Journal of Infectious Diseases, 211*(11), 1692-1702.

Background. Elite controllers spontaneously suppress human immunodeficiency virus (HIV) viremia but also demonstrate chronic inflammation that may increase risk of comorbid conditions. We compared hospitalization rates and causes among elite controllers to those of immunologically intact persons with medically controlled HIV. Methods. For adults in care at 11 sites from 2005 to 2011, person-years with CD4 T-cell counts ≥ 350 cells/mm2 were categorized as medical control, elite control, low viremia, or high viremia. All-cause and diagnostic category-specific hospitalization rates were compared between groups using negative binomial regression. Results. We identified 149 elite controllers (0.4%) among 34 354 persons in care. Unadjusted hospitalization rates among the medical control, elite control, low-viremia, and high-viremia groups were 10.5, 23.3, 12.6, and 16.9 per 100 person-years, respectively. After adjustment for demographic and clinical factors, elite control was associated with higher rates of all-cause (adjusted incidence rate ratio, 1.77 [95% confidence interval, 1.21-2.60]), cardiovascular (3.19 [1.50-6.79]) and psychiatric (3.98 [1.54-10.28]) hospitalization than was medical control. Non-AIDS-defining infections were the most common reason for admission overall (24.1% of hospitalizations) but were rare among elite controllers (2.7%), in whom cardiovascular hospitalizations were most common (31.1%). Conclusions. Elite controllers are hospitalized more frequently than persons with medically controlled HIV and cardiovascular hospitalizations are an important contributor.

Cservenka, A., Alarcón, G., Jones, S. A., & Nagel, B. J. (2015). Advances in human neuroconnectivity research: Applications for understanding familial history risk for alcoholism. *Alcohol Research: Current Reviews, 37*(1)

Recent advances in brain imaging have allowed researchers to further study the networks connecting brain regions. Specifically, research examining the functioning of these networks in groups with a genetic predisposition for alcoholism has found atypical circuitry in the brains of such individuals. Further research with larger sample sizes and multimodal method integration are necessary to confirm these intriguing findings. © 2015, National Institute on Alcohol Abuse and Alcoholism (NIAAA). All rights reserved.

Cui, C., Noronha, A., Warren, K. R., Koob, G. F., Sinha, R., Thakkar, M., et al. (2015). Brain pathways to recovery from alcohol dependence. *Alcohol (Fayetteville, N.Y.), 49*(5), 435-452.

This article highlights the research presentations at the satellite symposium on "Brain Pathways to Recovery from Alcohol Dependence" held at the 2013 Society for Neuroscience Annual Meeting. The purpose of this symposium was to provide an up to date overview of research efforts focusing on understanding brain mechanisms that contribute to recovery from alcohol dependence. A panel of scientists from the alcohol and addiction research field presented their insights and perspectives on brain mechanisms that may underlie both recovery and lack of recovery from alcohol dependence. The four sessions of the symposium encompassed multilevel studies exploring mechanisms underlying relapse and craving associated with sustained alcohol abstinence, cognitive function deficit and recovery, and translational studies on preventing relapse and promoting recovery. Gaps in our knowledge and research opportunities were also discussed.

Curtze, C., Nutt, J. G., Carlson-Kuhta, P., Mancini, M., & Horak, F. B. (2015). Levodopa is a double-edged sword for balance and gait in people with parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society,*

The effects of levodopa on balance and gait function in people with Parkinson's disease (PD) is controversial. This study compared the relative responsiveness to l-dopa on six domains of balance and gait: postural sway in stance; gait pace; dynamic stability; gait initiation; arm

swing; and turning in people with mild and severe PD, with and without dyskinesia. We studied 104 subjects with idiopathic PD (H & Y II [n = 52] and III-IV [n = 52]) and 64 age-matched controls. Subjects performed a mobility task in the practical off state and on l-dopa: standing quietly for 30 seconds, initiating gait, walking 7 meters, and turning 180 degrees. Thirty-four measures of mobility were computed from inertial sensors. Standardized response means were used to determine relative responsiveness to l-dopa. The largest improvements with l-dopa were found for arm swing and pace-related gait measures. Gait dynamic stability was unaffected by PD and not responsive to l-dopa. l-dopa reduced turning duration, but only in subjects with severe PD. In contrast to gait, postural sway in quiet standing increased with l-dopa, especially in the more severely affected subjects. The increase in postural sway, as well as decrease in turning duration and exaggerated arm swing with l-dopa was observed only for subjects with dyskinesia at the time of testing. The observed spectrum of l-dopa responsiveness in balance and gait measures suggests that multiple neural circuits control balance and gait. Many of the negative effects of l-dopa may be directly or indirectly caused by dyskinesia. (c) 2015 International Parkinson and Movement Disorder Society.

Cusanovich, D. A., Daza, R., Adey, A., Pliner, H. A., Christiansen, L., Gunderson, K. L., et al. (2015). Multiplex single-cell profiling of chromatin accessibility by combinatorial cellular indexing. *Science*, *348*(6237), 910-914.

Technical advances have enabled the collection of genome and transcriptome data sets with single-cell resolution. However, single-cell characterization of the epigenome has remained challenging. Furthermore, because cells must be physically separated before biochemical processing, conventional single-cell preparatory methods scale linearly. We applied combinatorial cellular indexing to measure chromatin accessibility in thousands of single cells per assay, circumventing the need for compartmentalization of individual cells. We report chromatin accessibility profiles from more than 15,000 single cells and use these data to cluster cells on the basis of chromatin accessibility landscapes. We identify modules of coordinately regulated chromatin accessibility at the level of single cells both between and within cell types, with a scalable method that may accelerate progress toward a human cell atlas.

Danve, A., Perry, L., & Deodhar, A. (2015). Use of belimumab throughout pregnancy to treat active systemic lupus erythematosus-A case report. *Seminars in Arthritis and Rheumatism*, *44*(2), 195-197.

Background: Pregnancy can lead to flares in systemic lupus erythematosus (SLE), and the presence of SLE in pregnancy could lead to a poor outcome for the mother and the fetus. Objective: To describe a patient whose active SLE (including lupus nephritis) was managed with the use of belimumab throughout pregnancy. Methods: A case report and review of relevant literature is presented. Results: A 38-year-old Caucasian woman with SLE was seen for advice regarding planning a pregnancy and management of her active lupus (cutaneous lupus, angioedema, lupus nephritis, leukopenia, and anti-phospholipid antibody syndrome) that could only be controlled by mycophenolate, a drug contraindicated in pregnancy. Azathioprine, hydroxychloroquine, rituximab, and moderate doses of prednisone were either unable to control her disease or led to unacceptable toxicity. After detailed discussions, she was treated with belimumab, which controlled her SLE and allowed withdrawal of mycophenolate. Belimumab was continued throughout the pregnancy, leading to well-controlled SLE and uneventful course, albeit with the presence of mild Ebstein's anomaly in the baby. Conclusion: To our knowledge, this is the first case report of belimumab use throughout pregnancy for controlling active SLE. Data from the belimumab pregnancy registry would be useful to confirm our findings and to further assess safety of this agent for use in pregnancy. © 2014 Elsevier Inc.

Dart, R. C., Bronstein, A. C., Spyker, D. A., Cantilena, L. R., Seifert, S. A., Heard, S. E., et al. (2015). Poisoning in the united states: 2012 emergency medicine report of the national poison data system. *Annals of Emergency Medicine*, *65*(4), 416-422.

Deaths from drug overdose have become the leading cause of injury death in the United States, where the poison center system is available to provide real-time advice and collect data about a variety of poisonings. In 2012, emergency medical providers were confronted with new poisonings, such as bath salts (substituted cathinones) and Spice (synthetic cannabinoid drugs), as well as continued trends in established poisonings such as from prescription opioids. This article addresses current trends in opioid poisonings; new substances implicated in poisoning cases, including unit-dose laundry detergents, bath salts, Spice, and energy drinks; and the role

of poison centers in public health emergencies such as the Fukushima radiation incident. © 2014 American College of Emergency Physicians.

Davis, C. M., Ammi, A. Y., Alkayed, N. J., & Kaul, S. (2015). Ultrasound stimulates formation and release of vasoactive compounds in brain endothelial cells. *American Journal of Physiology.Heart and Circulatory Physiology*, , ajpheart.00690.2014.

Stroke outcome is improved by therapeutic ultrasound. This benefit is presumed to be principally from ultrasound-mediated thrombolysis. We hypothesized that the therapeutic benefit of ultrasound in stroke may, in part, be mediated by release of beneficial vasoactive substances. Accordingly we investigated the effect of ultrasound on levels of cytochrome P450, lipoxygenase and cyclooxygenase metabolites of arachidonic acid as well as adenosine release and endothelial nitric oxide synthase (eNOS) phosphorylation in primary brain endothelial cells in-vitro. Brain endothelial cells were exposed to 1.05 MHz ultrasound at peak rarefactional acoustic pressure amplitudes of 0.35, 0.55, 0.90 and 1.30 MPa. Epoxyeicosatrienoic acids (EETs), hydroxyeicosatetraenoic acids (HETEs), prostaglandin E2 (PGE2), adenosine, nitrate/ nitrite and eNOS phosphorylation were measured after ultrasound exposure. Levels of 8,9-, 11,12- and 14,15-EET increased by 230 +/- 28%, 240+/- 30% and 246 +/- 31% ($p<0.05$) respectively, whereas 5- and 15-HETE levels were reduced to 24 +/- 14% and 10 +/- 3% ($p<0.05$), respectively, compared to cells not exposed to ultrasound. PGE2 levels were reduced to 56 +/- 14% of control. Adenosine increased more than six-fold following ultrasound exposure compared to unstimulated cells (1.36 +/- 0.22 ngmL-1 versus 0.37 +/- 0.10 ngmL-1, $p<0.05$), nitrate/ nitrite was below levels of quantification and eNOS phosphorylation was not altered significantly. Our results suggest that ultrasound may enhance tissue perfusion during stroke by augmenting the generation of vasodilator compounds and inhibiting that of vasoconstrictors. Such regulation supports a beneficial role for therapeutic ultrasound in stroke independent of its effect on the occlusive thrombus.

Davis, S. J., Lauer, A. K., & Flaxel, C. J. (2015). Reply. *Retina (Philadelphia, Pa.)*, *35*(7), e33-4.

de Oliveira, D. C., Ayres, A. P., Rocha, M. G., Giannini, M., Puppin Rontani, R. M., Ferracane, J. L., et al. (2015). Effect of different in vitro aging methods on color stability of a dental resin-based

composite using CIELAB and CIEDE2000 color-difference formulas. *Journal of Esthetic and Restorative Dentistry : Official Publication of the American Academy of Esthetic Dentistry ...[Et Al.]*,

PURPOSE: To evaluate the effect of different in vitro aging methods on color change (CC) of an experimental dental resin-based composite using CIELAB (DeltaEab) and CIEDE2000 (DeltaE00) color-difference formulas. MATERIALS AND METHODS: The CC was evaluated with a spectrophotometer (CM700d, Konica Minolta, Tokyo, Japan) according to the CIE chromatic space. Disk-shaped specimens (Phi = 5 x 1 mm thick) (N = 10) were submitted to different in vitro aging methods: 30 days of water aging (WA); 120 hours of ultraviolet light aging (UVA); or 300 hours of an accelerated artificial aging (AAA) method with cycles of 4 hours of UV-B light exposure and 4 hours of moisture condensation to induce CC. The temperature was standardized at 37 degrees C for all aging methods. CC was evaluated with DeltaEab and DeltaE00 formulas. Differences in individual Lab coordinates were also calculated. Data for the individual color parameters were submitted to one-way analysis of variance and Tukey's test for multiple comparisons (alpha = 0.05). RESULTS: All in vitro aging methods tested induced CC, in the following order: WA: DeltaEab = 0.83 (0.1); DeltaE00 = 1.15 (0.1) /=1; the methods with UV aging showed a yellowing effect due a large positive change in b*. CONCLUSIONS: All in vitro aging methods tested induced a CC, but to different extents. Changes in color followed similar trends, but with different absolute values when calculated with the CIELAB and the CIEDE2000 formulas. CLINICAL SIGNIFICANCE: Establishing the efficacy of different artificial aging methods and differences between color change using CIELAB and CIEDE2000 formulas are important to standardize color stability evaluations and facilitate the comparison of outcomes from different studies in the literature.

DeConde, A. S., Mace, J. C., Ashby, S., Smith, T. L., Orlandi, R. R., & Alt, J. A. (2015). Characterization of facial pain associated with chronic rhinosinusitis using validated pain evaluation instruments. *International Forum of Allergy & Rhinology*,

BACKGROUND: Prior investigations into facial pain associated with chronic rhinosinusitis (CRS) have yielded important results, but have yet to use pain-specific outcome measures. This study seeks to characterize facial pain associated with CRS using validated pain-specific instruments.

METHODS: Adults with CRS were enrolled into a prospective, cross-sectional study along with control participants presenting with non-CRS diagnoses. Facial pain was characterized in both groups using the Brief Pain Inventory Short Form (BPI-SF) and the Short-Form McGill Pain Questionnaire (SF-MPQ). CRS-specific measures of disease were measured including the 22-item Sino-Nasal Outcome Test-22 (SNOT-22), nasal endoscopy, and computed tomography scoring. RESULTS: The patients comprised of CRS with nasal polyposis (CRSwNP; n = 25), CRS without nasal polyposis (CRSsNP; n = 30), and control participants (n = 8). Subjects with CRSwNP and CRSsNP were less likely to be pain free than controls (16.0%, 6.7%, and 62.5% respectively, p = 0.001) and carried greater burden of pain as measured by the BPI-SF and SF-MPQ than controls (p = 0.002 and p = 0.017, respectively). Pain in CRS was most commonly located around the eyes and characterized as "throbbing" and "aching." Nasal polyp status was not associated with differences in character, severity, or location of pain. CONCLUSION: Subjects with CRS have a greater burden of facial pain relative to control subjects across several standardized pain measures. Further, facial pain in CRS significantly correlated to quality of life and CRS-specific disease severity measures. Study across larger cohorts using standardized pain measures is warranted to clarify the association of facial pain with CRS.

Delis, F., Rombola, C., Bellezza, R., Rosko, L., Grandy, D. K., Volkow, N. D., et al. (2015). Regulation of ethanol intake under chronic mild stress: Roles of dopamine receptors and transporters. *Frontiers in Behavioral Neuroscience*, *9*, 118.

Studies have shown that exposure to chronic mild stress decreases ethanol intake and preference in dopamine D2 receptor wild-type mice (Drd2 (+/+)), while it increases intake in heterozygous (Drd2 (+/-)) and knockout (Drd2 (-/-)) mice. Dopaminergic neurotransmission in the basal forebrain plays a major role in the reinforcing actions of ethanol as well as in brain responses to stress. In order to identify neurochemical changes associated with the regulation of ethanol intake, we used in vitro receptor autoradiography to measure the levels and distribution of dopamine D1 and D2 receptors and dopamine transporters (DAT). Receptor levels were measured in the basal forebrain of Drd2 (+/+), Drd2 (+/-), and Drd2 (-/-) mice belonging to one of four groups: control (C), ethanol intake (E), chronic mild stress exposure (S), and ethanol intake under chronic mild stress (ES). D2 receptor levels were higher in the lateral and medial

striatum of Drd2 (+/+) ES mice, compared with Drd2 (+/+) E mice. Ethanol intake in Drd2 (+/+) mice was negatively correlated with striatal D2 receptor levels. D2 receptor levels in Drd2(+/-) mice were the same among the four treatment groups. DAT levels were lower in Drd2(+/-) C and Drd2 (-/-) C mice, compared with Drd2 (+/+) C mice. Among Drd2(+/-) mice, S and ES groups had higher DAT levels compared with C and E groups in most regions examined. In Drd2(-/-) mice, ethanol intake was positively correlated with DAT levels in all regions studied. D1 receptor levels were lower in Drd2(+/-) and Drd2(-/-) mice, compared with Drd2(+/+), in all regions examined and remained unaffected by all treatments. The results suggest that in normal mice, ethanol intake is associated with D2 receptor-mediated neurotransmission, which exerts a protective effect against ethanol overconsumption under stress. In mice with low Drd2 expression, where DRD2 levels are not further modulated, ethanol intake is associated with DAT function which is upregulated under stress leading to ethanol overconsumption.

Dhingra, L. K., Lam, K., Cheung, W., Shao, T., Li, Z., Van de Maele, S., et al. (2015). Variation in symptom distress in underserved chinese american cancer patients. *Cancer*,

BACKGROUND: Cancer is prevalent in the rapidly growing Chinese American community, yet little is known about the symptom experience to guide comprehensive treatment planning. This study evaluated symptom prevalence and patient subgroups with symptom distress in a large sample of Chinese American cancer patients. METHODS: Patients were consecutively recruited from 4 oncology practices, and they completed a translated cancer symptom scale. Latent class cluster analysis was used to identify subgroups of patients with distinct symptom distress profiles. RESULTS: There were 1436 patients screened; 94.4% were non-English-speaking, and 45.1% were undergoing cancer therapy. The cancers included breast (32.6%), lung (14.8%), head and neck (12.5%), and hematologic cancer (10.1%). Overall, 1289 patients (89.8%) had 1 or more symptoms, and 1129 (78.6%) had 2 or more. The most prevalent symptoms were a lack of energy (57.0%), dry mouth (55.6%), feeling sad (49.3%), worrying (47.5%), and difficulty sleeping (46.8%). Symptoms causing "quite a bit" or "very much" distress included difficulty sleeping (37.9%), a lack of appetite (37.2%), feeling nervous (35.8%), pain (35.2%), and worrying (34.0%). Four patient subgroups were identified according to the probability of reporting moderate to high symptom distress: very low physical and psychological symptom

distress (49.5%), low physical symptom distress and moderate psychological symptom distress (25.2%), moderate physical and psychological symptom distress (17.4%), and high physical and psychological symptom distress (7.8%). CONCLUSIONS: Symptom prevalence is high in community-dwelling Chinese American cancer patients, and nearly half experience severe distress (rated as "quite a bit" or "very much" distressing) from physical symptoms, psychological symptoms, or both. These data have important implications for the development of effective symptom control interventions. Cancer 2015. (c) 2015 American Cancer Society.

Dilley, S., Newbill, C., Pejovic, T., & Munro, E. (2015). Two cases of endocervical villoglandular adenocarcinoma: Support for conservative management. *Gynecologic Oncology Reports, 12*, 34-36.

*We describe two cases of villoglandular adenocarcinoma and review the literature.*This subtype may be treated more conservatively but few papers have described this.*Conservative management may be preferable for women who desire fertility.*Our experience shows successful treatment of VGA with CKC and simple hysterectomy.

Dobscha, S. K., Morasco, B. J., Kovas, A. E., Peters, D. M., Hart, K., & Mcfarland, B. H. (2015). Short-term variability in outpatient pain intensity scores in a national sample of older veterans with chronic pain. *Pain Medicine (United States), 16*(5), 855-865.

Objective: The Department of Veterans Affairs (VA) uses the 11-point pain numeric rating scale (NRS) to gather pain intensity information from veterans at outpatient appointments. Yet, little is known about how NRS scores may vary over time within individuals; NRS variability may have important ramifications for treatment planning. Our main objective was to describe variability in NRS scores within a 1-month timeframe, as obtained during routine outpatient care in older patients with chronic pain treated in VA hospitals. A secondary objective was to explore for patient characteristics associated with within-month NRS score variability. Design: Retrospective cohort study. Subjects: National sample of veterans 65 years or older seen in VA in 2010 who had multiple elevated NRS scores indicating chronic pain. Methods: VA datasets were used to identify the sample and demographic and clinical variables including NRS scores. For the main analysis, we identified subjects with two or more NRS scores obtained in each of two or more

months in a 12-month period; we examined ranges in NRS scores across the first two qualifying months. Results: Among 4,336 individuals in the main analysis cohort, the mean and median of the average NRS score range across the 2 months were 2.7 and 2.5, respectively. In multivariable models, main significant predictors of within-month NRS score variability were baseline pain intensity, overall medical comorbidity, and being divorced/separated. Conclusions: The majority of patients in the sample had clinically meaningful variation in pain scores within a given month. This finding highlights the need for clinicians and their patients to consider multiple NRS scores when making chronic pain treatment decisions.

Dombernowsky, S. L., Samsoe-Petersen, J., Petersen, C. H., Instrell, R., Hedegaard, A. M., Thomas, L., et al. (2015). The sorting protein PACS-2 promotes ErbB signalling by regulating recycling of the metalloproteinase ADAM17. *Nature Communications*, *6*, 7518.

The metalloproteinase ADAM17 activates ErbB signalling by releasing ligands from the cell surface, a key step underlying epithelial development, growth and tumour progression. However, mechanisms acutely controlling ADAM17 cell-surface availability to modulate the extent of ErbB ligand release are poorly understood. Here, through a functional genome-wide siRNA screen, we identify the sorting protein PACS-2 as a regulator of ADAM17 trafficking and ErbB signalling. PACS-2 loss reduces ADAM17 cell-surface levels and ADAM17-dependent ErbB ligand shedding, without apparent effects on related proteases. PACS-2 co-localizes with ADAM17 on early endosomes and PACS-2 knockdown decreases the recycling and stability of internalized ADAM17. Hence, PACS-2 sustains ADAM17 cell-surface activity by diverting ADAM17 away from degradative pathways. Interestingly, Pacs2-deficient mice display significantly reduced levels of phosphorylated EGFR and intestinal proliferation. We suggest that this mechanism controlling ADAM17 cell-surface availability and EGFR signalling may play a role in intestinal homeostasis, with potential implications for cancer biology.

Edwards, S. T., Rubenstein, L. V., Meredith, L. S., Hackbarth, N. S., Stockdale, S. E., Cordasco, K. M., et al. (2015). Who is responsible for what tasks within primary care: Perceived task allocation among primary care providers and interdisciplinary team members. *Healthcare*,

Background: Unclear roles in interdisciplinary primary care teams can impede optimal team-based care. We assessed perceived task allocation among primary care providers (PCPs) and staff during implementation of a new patient-centered care model in Veterans Affairs (VA) primary care practices. Methods: We performed a cross-sectional survey of PCPs and primary care staff (registered nurses (RNs), licensed practical/vocational nurses (LPNs), and medical assistants/clerks (MAs)) in 23 primary care practices within one VA region. We asked subjects whether PCPs performed each of 14 common primary care tasks alone, or relied upon staff for help. Tasks included gathering preventive service history, disease screening, evaluating patients and making treatment decisions, intervening on lifestyle factors, educating patients about self-care activities and medications, refilling prescriptions, receiving and resolving patient messages, completing forms, tracking diagnostic data, referral tracking, and arranging home health care. We then performed multivariable regression to determine predictors of perceived PCP reliance on staff for each task. Results: 162 PCPs and 257 staff members responded, a 60% response rate. For 12/14 tasks, fewer than 50% of PCPs reported relying on staff for help. For all 14 tasks, over 85% of RNs reported they were relied upon. For 12/14 tasks, over 50% of LPNs reported they were relied on, while for 5/14 tasks a majority of MAs reported being relied upon. Nurse practitioners and physician assistants (NP/PAs) reported relying on staff less than physicians. Conclusions: Early in the implementation of a team-based primary care model, most PCPs perceived they were solely responsible for most clinical tasks. RNs, and LPNs felt they were relied upon for most of the same tasks, while medical assistants/clerks reported being relied on for fewer tasks. Better understanding of optimal inter-professional team task allocation in primary care is needed. © 2015.

Elsawy, M., Storer, B. E., Pulsipher, M. A., Maziarz, R. T., Bhatia, S., Maris, M. B., et al. (2015). Multi-centre validation of the prognostic value of the haematopoietic cell transplantation- specific comorbidity index among recipient of allogeneic haematopoietic cell transplantation. *British Journal of Haematology*,

The haematopoietic cell transplantation-specific comorbidity index (HCT-CI) was developed in a single centre as a weighted scoring system to predict risks of non-relapse mortality (NRM) following allogeneic haematopoietic cell transplantation. Information on the performance of the

HCT-CI in multi-centre studies is lacking in the literature. To that end, a collaborative multicentre retrospective study was initiated. Comorbidity data from 2523 consecutive recipients of human leucocyte antigen-matched grafts from five different US institutions were analysed. Among all patients, HCT-CI scores of 0 vs. 1-2 vs. ≥3 were associated with 2-year NRM rates of 14%, 23% and 39% (P < 0·0001), respectively, and 2-year overall survival (OS) rates of 74%, 61% and 39%, respectively (P < 0·0001). Using regression models, increasing HCT-CI scores were independently associated with increases in hazard ratios for NRM and worse survival within individual institutions. The HCT-CI retained independent capacity for association with outcomes within different age as well as conditioning intensity groups. C-statistic estimates for the prognostic power of the HCT-CI for NRM and OS were 0·66 and 0·64, respectively. The estimates within each institution were overall similar. The HCT-CI is a valid tool for capturing comorbidities and predicting mortality after haematopoietic cell transplantation across different institutions. © 2015 John Wiley & Sons Ltd.

England, B. R., Sayles, H., Michaud, K., Caplan, L., Davis, L. A., Cannon, G. W., et al. (2015). Cause-specific mortality in US veteran men with rheumatoid arthritis. *Arthritis Care & Research*,
OBJECTIVE: There has been limited investigation into cause-specific mortality and the associated risk factors in men with rheumatoid arthritis (RA). We investigated all-cause and cause-specific mortality in men with RA, examining determinants of survival. METHODS: Men from a longitudinal RA registry were followed from enrollment until death or through 2013. Vital status and cause of death were determined using the National Death Index. Crude mortality rates and standardized mortality ratios (SMRs) were calculated for all-cause, cardiovascular disease (CVD), cancer, and respiratory mortality. Associations with all-cause and cause-specific mortality were examined using multivariable Cox proportional hazards and competing-risks regression. RESULTS: There were 1,652 men with RA and 332 deaths. CVD (31.6%; SMR 1.77, 95% CI 1.46-2.14), cancer (22.9%; SMR 1.50; 95% CI 1.20-1.89), and respiratory disease (15.1%; SMR 2.90; 95% CI 2.20-3.83) were the leading causes of death. Factors associated with all-cause mortality included older age, Caucasian race, smoking, low body weight, comorbidity, disease activity, and prednisone use. Rheumatoid factor concentration was associated with CVD mortality, while nodules were associated with CVD and respiratory mortality. There were no

associations of methotrexate or biologic use with all-cause or cause-specific mortality. CONCLUSIONS: Men in this RA cohort experienced increased all-cause and cause-specific mortality, with a 3-fold risk of respiratory-related deaths compared to age-matched men in the general population. Further studies are needed to examine whether interventions targeting potentially "modifiable" correlates of mortality might lead to improved long-term survival in men with RA. This article is protected by copyright. All rights reserved.

Faggi, F., Codenotti, S., Poliani, P. L., Cominelli, M., Chiarelli, N., Colombi, M., et al. (2015). MURC/cavin-4 is co-expressed with caveolin-3 in rhabdomyosarcoma tumors and its silencing prevents myogenic differentiation in the human embryonal RD cell line. *PloS One*, *10*(6), e0130287.

The purpose of this study was to investigate whether MURC/cavin-4, a plasma membrane and Z-line associated protein exhibiting an overlapping distribution with Caveolin-3 (Cav-3) in heart and muscle tissues, may be expressed and play a role in rhabdomyosarcoma (RMS), an aggressive myogenic tumor affecting childhood. We found MURC/cavin-4 to be expressed, often concurrently with Cav-3, in mouse and human RMS, as demonstrated through in silico analysis of gene datasets and immunohistochemical analysis of tumor samples. In vitro expression studies carried out using human cell lines and primary mouse tumor cultures showed that expression levels of both MURC/cavin-4 and Cav-3, while being low or undetectable during cell proliferation, became robustly increased during myogenic differentiation, as detected via semi-quantitative RT-PCR and immunoblotting analysis. Furthermore, confocal microscopy analysis performed on human RD and RH30 cell lines confirmed that MURC/cavin-4 mostly marks differentiated cell elements, colocalizing at the cell surface with Cav-3 and labeling myosin heavy chain (MHC) expressing cells. Finally, MURC/cavin-4 silencing prevented the differentiation in the RD cell line, leading to morphological cell impairment characterized by depletion of myogenin, Cav-3 and MHC protein levels. Overall, our data suggest that MURC/cavin-4, especially in combination with Cav-3, may play a consistent role in the differentiation process of RMS.

Fay, J. F., & Farrens, D. L. (2015). Structural dynamics and energetics underlying allosteric inactivation of the cannabinoid receptor CB1. *Proceedings of the National Academy of Sciences of*

the United States of America,

G protein-coupled receptors (GPCRs) are surprisingly flexible molecules that can do much more than simply turn on G proteins. Some even exhibit biased signaling, wherein the same receptor preferentially activates different G-protein or arrestin signaling pathways depending on the type of ligand bound. Why this behavior occurs is still unclear, but it can happen with both traditional ligands and ligands that bind allosterically outside the orthosteric receptor binding pocket. Here, we looked for structural mechanisms underlying these phenomena in the marijuana receptor CB1. Our work focused on the allosteric ligand Org 27569, which has an unusual effect on CB1-it simultaneously increases agonist binding, decreases G-protein activation, and induces biased signaling. Using classical pharmacological binding studies, we find that Org 27569 binds to a unique allosteric site on CB1 and show that it can act alone (without need for agonist cobinding). Through mutagenesis studies, we find that the ability of Org 27569 to bind is related to how much receptor is in an active conformation that can couple with G protein. Using these data, we estimated the energy differences between the inactive and active states. Finally, site-directed fluorescence labeling studies show the CB1 structure stabilized by Org 27569 is different and unique from that stabilized by antagonist or agonist. Specifically, transmembrane helix 6 (TM6) movements associated with G-protein activation are blocked, but at the same time, helix 8/TM7 movements are enhanced, suggesting a possible mechanism for the ability of Org 27569 to induce biased signaling.

Feeney, M. P., Sanford, C. A., & Putterman, D. B. (2014). Effects of ear-canal static pressure on pure-tone thresholds and wideband acoustic immittance. *Journal of the American Academy of Audiology*, *25*(5), 462-470.

Background: Wideband acoustic immittance (WAI) measures provide information about middle-ear function across the traditional audiometric frequency range from 0.25 to 8.0 kHz. Recent studies have found that WAI is effective in predicting the presence of conductive hearing loss (CHL). It is not known whether WAI can accurately estimate the degree of threshold shift caused by CHL. Purpose: The purpose of the present study was to evaluate the relationship between changes in puretone threshold and changes in wideband absorbance and acoustic conductance levels induced by positive and negative ear-canal static pressure. Study Sample: Twenty young

adult subjects with normal hearing and a negative history of middle-ear disorders participated in the study. Data Collection and Analysis: Experimental pure-tone thresholds at 0.5 and 2.0 kHz were estimated by using a three-interval, three-alternative forced-choice adaptive psychometric procedure under three conditions: ambient ear-canal pressure, +200 daPa static pressure, and -200 daPa static pressure. Wideband absorbance and conductance were obtained in the same subjects by using a Welch Allyn prototype diagnostic middle ear analyzer. Changes in pure-tone threshold from the ambient pressure condition to the static pressure condition were evaluated by using a paired-samples t test and Pearson productmoment correlation. Results: Wideband middle-ear absorbance and conductance at ambient pressure in this study were consistent with published data in adults with normal hearing. The mean change in threshold at 0.5 and 2.0 kHz with +200 daPa or -200 daPa ear-canal static pressure was similar to the mean change in absorbance and conductance levels in the same conditions. However, there was one statistically significant difference between the shift in pure-tone threshold and the change in conductance level for the +200 daPa pressure condition for 2.0 kHz, with the change in threshold being 1.5 dB greater than the change in conductance level ($t = 2.39$, $p = 0.03$). In contrast to the good performance of WAI measures in predicting mean threshold shifts caused by ear-canal pressure, the shifts in WAI were not correlated with threshold shifts. Thus WAI was not well suited to predict individual threshold changes caused by earcanal static pressure. Conclusions: For the conditions of this study, results suggest that mean change in absorbance or conductance level caused by ear-canal static pressure of +200 daPa or -200 daPa provides a good estimate of the change in pure-tone threshold in the same conditions. However, individual threshold change was not accurately predicted by the change in absorbance or conductance level.

Feeney, M. P., Stover, B., Keefe, D. H., Garinis, A. C., Day, J. E., & Seixas, N. (2014). Sources of variability in wideband energy reflectance measurements in adults. *Journal of the American Academy of Audiology*, *25*(5), 449-461.

Background: Wideband acoustic immittance measurements of the middle ear, such as wideband energy reflectance (ER), can provide information about how the middle ear functions across the traditional audiometric frequency range. These measurements are being investigated as a new means of evaluating conductive hearing disorders, and studies have been reported on a number

of middle-ear disorders. However, the normative database for wideband ER is still being developed, and more information is needed about sources of test variability. Purpose: The purpose of the present study was to evaluate sources of variability in wideband ER measurements at baseline and across annual tests for up to 5 yr in subjects with normal hearing. Study Sample: The main group consisted of 112 subjects (187 ears), 24 females and 88 males, with normal hearing and normal 0.226-kHz admittance tympanometry. An additional 24 adults with abnormal 0.226-kHz tympanometry provided baseline comparison data. Research Design: A longitudinal design was used in obtaining annual measurements of audiometry, tympanometry, and wideband ER at ambient pressure in adults. Data Collection and Analysis: Clinical audiometry and tympanometry data and 1/3-octave wideband ER measurements were obtained at baseline and annually for up to four additional tests. Descriptive statistics and t-tests were used to explore differences in 1/3-octave baseline ER measures in terms of subject age, test ear, sex, and clinical tympanometry. Longitudinal mixed-effects linear regression models at 1.0, 2.0, and 4.0 kHz were used to examine the different sources of variance affecting ER over time. Results: There were small but statistically significant mean differences in ER for baseline measurements as a function of ear, sex, and age. Compared with these results, data for 29 ears with abnormal 0.226-kHz tympanometry differed from mean normal data across a broad frequency range by as much as 20%. ER varied as a function of peak compensated static acoustic admittance (Ytm) for measures at 1.0 kHz but was unrelated to Ytm at 2.0 and 4.0 kHz. ER also varied as a function of the test ear, with significantly higher ER on the left at 1.0 and 2.0 kHz, but was not significantly related to the test ear at 4.0 kHz. The standard deviation for test-retest variability was about 0.1 at each frequency, which is consistent with previous studies. Conclusions: Mean wideband ER at baseline showed small but significant differences related to sex, ear, and age. ERwas significantly related to Ytm at 1.0 kHzin the longitudinal data but not at 2.0 or 4.0 kHz and to the test ear at 1.0 and 2.0 kHz but not at4.0 kHz. When evaluated at ambient pressure, ER for ears with negative middle-ear pressure was similar to that of ears with abnormally low Ytm. Therefore it might be necessary to evaluate wideband acoustic immittance compensated for middle-ear pressure by using tympanometry to obtain an effective differential diagnosis of middle-ear disorders in adults.

Ferencik, M., & Chatzizisis, Y. S. (2015). Statins and the coronary plaque calcium "paradox": Insights from non-invasive and invasive imaging. *Atherosclerosis*,

Fling, B. W., Gera Dutta, G., & Horak, F. B. (2015). Functional connectivity underlying postural motor adaptation in people with multiple sclerosis. *NeuroImage.Clinical*, *8*, 281-289.

A well-characterized neural network is associated with motor learning, involving several brain regions known to have functional and structural deficits in persons with multiple sclerosis (PwMS). However, it is not known how MS affects postural motor learning or the neural networks involved. The aim of this study was to gain a better understanding of the neural networks underlying adaptation of postural responses within PwMS. Participants stood on a hydraulically driven, servo-controlled platform that translated horizontally forward and backward in a continuous sinusoidal pattern across multiple trials over two consecutive days. Our results show similar postural adaptation between PwMS and age-matched control participants despite overall deficits in postural motor control in PwMS. Moreover, PwMS demonstrated better retention the following day. PwMS had significantly reduced functional connectivity within both the cortico-cerebellar and cortico-striatal motor loops; neural networks that subserve implicit motor learning. In PwMS, greater connectivity strength within the cortico-cerebellar circuit was strongly related to better baseline postural control, but not to postural adaptation as it was in control participants. Further, anti-correlated cortico-striatal connectivity within the right hemisphere was related to improved postural adaptation in both groups. Taken together with previous studies showing a reduced reliance on cerebellar- and proprioceptive-related feedback control in PwMS, we suggest that PwMS may rely on cortico-striatal circuitry to a greater extent than cortico-cerebellar circuitry for the acquisition and retention of motor skills.

Fling, B. W., Nutt, J. G., & Horak, F. B. (2015). Reply: Does dominant pedunculopontine nucleus exist? probably not. *Brain : A Journal of Neurology*, *138*(Pt 5), e347.

Forrest, G. N., Bhalla, P., Debess, E. E., Winthrop, K. L., Lockhart, S. R., Mohammadi, J., et al. (2015). Cryptococcus gattii infection in solid organ transplant recipients: Description of oregon outbreak cases. *Transplant Infectious Disease*, *17*(3), 467-476.

Cryptococcus gattii was recognized as an emerging infection in the Pacific Northwest in 2004. Out

of 62 total infections in Oregon since the outbreak, 11 were in solid organ transplant (SOT) recipients. SOT recipients were more likely to have disseminated disease and higher mortality than normal hosts, who mostly had isolated mass lesions. The median time from transplantation to C. gattii diagnosis was 17.8 months. The primary sites of infection were lung (n = 4), central nervous system (n = 3), or both (n = 4). The Oregon-endemic strain, VGII (subtypes IIa and IIc) was present in 10 of 11 patients; the median fluconazole minimum inhibitory concentration (MIC) was 12 μg/mL (range 2-32 μg/mL) for this strain. We found C. gattii infection among organ transplant recipients was disseminated at diagnosis, had low cerebrospinal fluid cryptococcal antigen titers, and was associated with an elevated fluconazole MIC and high attributable mortality.

Franceschi, V., Parker, S., Jacca, S., Crump, R. W., Doronin, K., Hembrador, E., et al. (2015). BoHV-4-based vector single heterologous antigen delivery protects STAT1(-/-) mice from monkeypoxvirus lethal challenge. *PLoS Neglected Tropical Diseases, 9*(6), e0003850.

Monkeypox virus (MPXV) is the etiological agent of human (MPX). It is an emerging orthopoxvirus zoonosis in the tropical rain forest of Africa and is endemic in the Congo-basin and sporadic in West Africa; it remains a tropical neglected disease of persons in impoverished rural areas. Interaction of the human population with wildlife increases human infection with MPX virus (MPXV), and infection from human to human is possible. Smallpox vaccination provides good cross-protection against MPX; however, the vaccination campaign ended in Africa in 1980, meaning that a large proportion of the population is currently unprotected against MPXV infection. Disease control hinges on deterring zoonotic exposure to the virus and, barring that, interrupting person-to-person spread. However, there are no FDA-approved therapies against MPX, and current vaccines are limited due to safety concerns. For this reason, new studies on pathogenesis, prophylaxis and therapeutics are still of great interest, not only for the scientific community but also for the governments concerned that MPXV could be used as a bioterror agent. In the present study, a new vaccination strategy approach based on three recombinant bovine herpesvirus 4 (BoHV-4) vectors, each expressing different MPXV glycoproteins, A29L, M1R and B6R were investigated in terms of protection from a lethal MPXV challenge in STAT1 knockout mice. BoHV-4-A-CMV-A29LgD106DeltaTK, BoHV-4-A-EF1alpha-M1RgD106DeltaTK and

BoHV-4-A-EF1alpha-B6RgD106DeltaTK were successfully constructed by recombineering, and their capacity to express their transgene was demonstrated. A small challenge study was performed, and all three recombinant BoHV-4 appeared safe (no weight-loss or obvious adverse events) following intraperitoneal administration. Further, BoHV-4-A-EF1alpha-M1RgD106DeltaTK alone or in combination with BoHV-4-A-CMV-A29LgD106DeltaTK and BoHV-4-A-EF1alpha-B6RgD106DeltaTK, was shown to be able to protect, 100% alone and 80% in combination, STAT1(-/-) mice against mortality and morbidity. This work demonstrated the efficacy of BoHV-4 based vectors and the use of BoHV-4 as a vaccine-vector platform.

Fried-Oken, M., Daniels, D., Ettinger, O., Mooney, A., Noethe, G., & Rowland, C. (2015). What's on your mind? conversation topics chosen by people with degenerative cognitive-linguistic disorders for communication boards. *American Journal of Speech-Language Pathology*, *24*(2), 272-280. Purpose: Conversational topics chosen by a group of adults with degenerative cognitive-linguistic disorders for personalized communication board development were examined. The patient-generated themes commonly selected are presented to guide treatment planning and communication board development. Method: Communication boards were created for 109 adults as part of a larger research project. One autobiographical topic that each participant would enjoy discussing multiple times was represented on each communication board with 16 pictures and word labels. For this review, topics were collapsed into general themes through a consens us process and examined by gender and age. Results: Sixty unique conversational topics were identified from 109 participants and collapsed into 9 general themes: Hobbies, Family, Travel, Work, Home/Places I've Lived, Sports/Fitness, Religion, Animals, and World War II. Age and gender produced variations in themes chosen, though no significance in rank orders was found across groups. Conclusions: Topics selected by adults with degenerative cognitive-linguistic disorders for communication boards resemble common conversational adult themes and do not center around basic needs or medical issues. Differences in gender and age for topic selection tend to be based on traditional roles. These general themes should be used when creating personalized communication boards for those who benefit from conversational aids.

Froemke, C. C., Wang, L., DeHart, M. L., Williamson, R. K., Ko, L. M., & Duwelius, P. J. (2015). Standardizing care and improving quality under a bundled payment initiative for total joint arthroplasty. *The Journal of Arthroplasty*,

Increasing demands for episodic bundled payments in total hip and knee arthroplasty are motivating providers to wring out inefficiencies and coordinate services. This study describes a care pathway and gainshare arrangement as the mechanism by which improvements in efficiency were realized under a bundled payment pilot. Analysis of cut-to-close time, LOS, discharge destination, implant cost, and total allowed claims between pre-pilot and pilot cohorts showed an 18% reduction in average LOS (70.8 to 58.2 hours) and a shift from home health and skilled nursing facility discharge to home self-care (54.1% to 63.7%). No significant differences were observed for cut-to-close time and implant cost. Improvements resulted in a 6% reduction in the average total allowed claims per case.

Fu, X. W., Song, P. F., & Spindel, E. R. (2015). Role of Lynx1 and related Ly6 proteins as modulators of cholinergic signaling in normal and neoplastic bronchial epithelium. *International Immunopharmacology*,

The ly-6 proteins are a large family of proteins that resemble the snake three finger alpha toxins such as alpha-bungarotoxin and are defined by their multiple cysteine residues. Multiple members of the ly-6 protein family can modulate nicotinic signaling including lynx1, lynx2, slurp-1, slurp-2 and prostate stem cell antigen (PSCA). Consistent with the expression of multiple nicotinic receptors in bronchial epithelium, multiple members of the nicotinic-modulatory ly-6 proteins are expressed in lung including lynx1 and lynx2. We studied the role of lynx1 as an exemplar of the role of ly-6 proteins in lung. Our data demonstrates that lynx1 acts as a negative modulator of nicotinic signaling in normal and neoplastic lung. In normal lung lynx1 serves to limit the ability of chronic nicotine exposure to increase levels of nicotinic receptors and also serves to limit the ability of nicotine to upregulate levels of GABAA receptors in lung. In turn this allows lynx1 to limit the ability of nicotine to upregulate levels of mucin which is mediated by GABAergic signaling. This suggests that lynx1-mimetics may have potential for treatment of asthma and COPD. In that most lung cancer cells also express nicotinic receptor and lynx1 we examined the role of lynx-1 in lung cancer. Lynx1 levels are decreased in lung cancers compared

to adjacent normal lung. Knockdown of lynx1 by siRNAs increased growth of lung cancer cells while expression of lynx1 in lung cancer cell decreased cell proliferation. This suggests that lynx1 is an endogenous regulator of lung cancer growth. Given that multiple small molecule negative and positive allosteric modulators of nicotinic receptors have already been developed, this suggests that lynx1 is a highly druggable target both for development of drugs that may limit lung cancer growth as well as for drugs that may be effective for asthma or COPD treatment.

Fujii, A., Shearer, T. R., & Azuma, M. (2015). Galectin-3 enhances extracellular matrix associations and wound healing in monkey corneal epithelium. *Experimental Eye Research, 137*, 71-78.
Poor healing of epithelial wounds in cornea is a major clinical problem, leading to persistent epithelial defects and ulceration. The primary cause is poor cell migration over the wound. Carbohydrate-binding protein galectin-3 binds to extracellular matrixes (ECMs) and promotes lamellipodia formation by cross-linking to alpha3 integrin. Recombinant galectin-3 also facilitates wound healing in the rodent cornea. The purposes of the present experiments were to: (1) establish epithelial wound healing models in monkey corneal explant culture, the models more relevant to human, (2) evaluate the healing effect of galectin-3 in our models, and (3) determine if galectin-3 enhances cell adhesion by interacting with ECMs on corneal surface and their ligand integrins. Monkey corneas with central wounds produced by sodium hydroxide (NaOH) or n-heptanol were incubated with or without recombinant galectin-3. The defected area was stained with sodium fluorescein. Primary isolated corneal epithelial cells from monkey were cultured with or without galectin-3 on plates coated with ECMs or integrins, and the number of adhering cells was counted. Galectin-3 expression in various eye tissues was visualized by immunoblotting. NaOH caused loss of epithelial cells and basement membrane. n-Heptanol removed epithelial cells, but the basement membrane was retained. These corneal defects spontaneously became smaller in a time-dependent manner. Exogenous galectin-3 enhanced wound healing in both NaOH and n-heptanol models. Galectin-3 also enhanced cell adhesion onto the major ECMs found in the basement and Bowman's membranes and onto integrins. Relatively high levels of galectin-3 were detected in corneal and conjunctival epithelium, but tear fluid contained negligible galactin-3. These results suggested that the enhanced binding of epithelial cells to ECMs and integrins caused by galectin-3 might promote cell migration over wounded corneal surfaces.

Since tear fluid contained relatively low levels of galectin-3, exogenous galectin-3 may be a beneficial drug to enhance re-epithelialization in human corneal diseases.

Galivo, F. H., Dorrell, C. S., Grompe, M., Zhong, Y. P., Streeter, P., & Grompe, M. (2015). Novel surface markers directed against adult human gallbladder. *Stem Cell Research, 15*(1), 172-181.
Novel cell surface-reactive monoclonal antibodies generated against extrahepatic biliary cells were developed for the isolation and characterization of different cell subsets from normal adult human gallbladder. Eleven antigenically distinct gallbladder subpopulations were isolated by fluorescence-activated cell sorting. They were classified into epithelial, mesenchymal, and pancreatobiliary (PDX1+SOX9+) subsets based on gene expression profiling. These antigenically distinct human gallbladder cell subsets could potentially also reflect different functional properties in regards to bile physiology, cell renewal and plasticity. Three of the novel monoclonal antibodies differentially labeled archival sections of primary carcinoma of human gallbladder relative to normal tissue. The novel monoclonal antibodies described herein enable the identification and characterization of antigenically diverse cell subsets within adult human gallbladder and are putative tumor biomarkers.

Gavin, D. P., Kusumo, H., Sharma, R. P., Guizzetti, M., Guidotti, A., & Pandey, S. C. (2015). Gadd45b and N-methyl-d-aspartate induced DNA demethylation in postmitotic neurons. *Epigenomics, 7*(4), 567-579.
AIM: In nondividing neurons examine the role of Gadd45b in active 5-methylcytosine (5MC) and 5-hydroxymethylcytosine (5HMC) removal at a gene promoter highly implicated in mental illnesses and cognition, Bdnf. MATERIALS & METHODS: Mouse primary cortical neuronal cultures with and without Gadd45b siRNA transfection were treated with N-methyl-d-aspartate (NMDA). Expression changes of genes reportedly involved in DNA demethylation, Bdnf mRNA and protein and 5MC and 5HMC at Bdnf promoters were measured. RESULTS: Gadd45b siRNA transfection in neurons abolishes the NMDA-induced increase in Bdnf IXa mRNA and reductions in 5MC and 5HMC at the Bdnf IXa promoter. CONCLUSION: These results contribute to our understanding of DNA demethylation mechanisms in neurons, and its role in regulating NMDA responsive genes implicated in mental illnesses.

Gillessen, S., Omlin, A., Attard, G., de Bono, J. S., Efstathiou, E., Fizazi, K., et al. (2015). Management of patients with advanced prostate cancer: Recommendations of the st.gallen advanced prostate cancer consensus conference (APCCC) 2015. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO,*

The first St.Gallen Advanced Prostate Cancer Consensus Conference (APCCC) Expert Panel identified and reviewed the available evidence for the ten most important areas of controversy in advanced prostate cancer management. The successful registration of several drugs for castration-resistant prostate cancer and the recent studies of chemo-hormonal therapy in men with castration-naive prostate cancer have led to considerable uncertainty as to the best treatment choices, sequence of treatment options and appropriate patient selection.Management recommendations based on expert opinion, and not based on a critical review of the available evidence, are presented. The various recommendations carried differing degrees of support, as reflected in the wording of the article text and in the detailed voting results recorded in supplementary material, available at Annals of Oncology online. Detailed decisions on treatment as always will involve consideration of disease extent and location, prior treatments, host factors, patient preferences as well as logistical and economic constraints. Inclusion of men with advanced prostate cancer in clinical trials should be encouraged.

Givi, B., Troob, S. H., Stott, W., Cordeiro, T., Andersen, P. E., & Gross, N. D. (2015). Transoral robotic retropharyngeal node dissection. *Head & Neck,*

BACKGROUND: Surgical access to metastases in the retropharyngeal lymph nodes (RPLN) could be difficult. Transoral robotic surgery (TORS) can be utilized to access RPLNs. The purpose of this study was to describe a TORS approach to RPLN dissection. METHODS: Case series of patients undergoing RPLN dissection by TORS, compared to matched controls (1:2). RESULTS: Twelve patients underwent robotic RPLN dissection. Median age was 63 (43-73). Pathology was oropharyngeal squamous cell carcinoma (OPSCC) in 9 and papillary thyroid cancer (PTC) in 3. The feeding tube dependence length was 12 days (1-46) on average. Complications occurred in 8 (66%); most commonly, aspiration pneumonitis (6). In comparison to the matched controls (24), there was no difference in length of stay or feeding tube dependence. Complications were higher in OPSCC patients. CONCLUSION: TORS is feasible for accessing RPLN. The procedure is well

tolerated in PTC patients; OPSCC patients are at increased risk of complications.

Gold, R., Nelson, C., Cowburn, S., Bunce, A., Hollombe, C., Davis, J., et al. (2015). Feasibility and impact of implementing a private care system's diabetes quality improvement intervention in the safety net: A cluster-randomized trial. *Implementation Science : IS*, *10*(1), 83-015-0259-4. BACKGROUND: Integrated health care delivery systems devote considerable resources to developing quality improvement (QI) interventions. Clinics serving vulnerable populations rarely have the resources for such development but might benefit greatly from implementing approaches shown to be effective in other settings. Little trial-based research has assessed the feasibility and impact of such cross-setting translation and implementation in community health centers (CHCs). We hypothesized that it would be feasible to implement successful QI interventions from integrated care settings in CHCs and would positively impact the CHCs. METHODS: We adapted Kaiser Permanente's successful intervention, which targets guideline-based cardioprotective prescribing for patients with diabetes mellitus (DM), through an iterative, stakeholder-driven process. We then conducted a cluster-randomized pragmatic trial in 11 CHCs in a staggered process with six "early" CHCs implementing the intervention one year before five "'late" CHCs. We measured monthly rates of patients with DM currently prescribed angiotensin converting enzyme (ACE)-inhibitors/statins, if clinically indicated. Through segmented regression analysis, we evaluated the intervention's effects in June 2011-May 2013. Participants included ~6500 adult CHC patients with DM who were indicated for statins/ACE-inhibitors per national guidelines. RESULTS: Implementation of the intervention in the CHCs was feasible, with setting-specific adaptations. One year post-implementation, in the early clinics, there were estimated relative increases in guideline-concordant prescribing of 37.6 % (95 % confidence interval (CI); 29.0-46.2 %) among patients indicated for both ACE-inhibitors and statins and 38.7 % (95 % CI; 23.2-54.2 %) among patients indicated for statins. No such increases were seen in the late (control) clinics in that period. CONCLUSIONS: To our knowledge, this was the first clinical trial testing the translation and implementation of a successful QI initiative from a private, integrated care setting into CHCs. This proved feasible and had significant impact but required considerable adaptation and implementation support. These results suggest the feasibility of adapting diverse

strategies developed in integrated care settings for implementation in under-resourced clinics, with important implications for efficiently improving care quality in such settings. CLINICALTRIALS.GOV: NCT02299791 .

Gomez, J. L., Cunningham, C. L., Finn, D. A., Young, E. A., Helpenstell, L. K., Schuette, L. M., et al. (2015). Differential effects of ghrelin antagonists on alcohol drinking and reinforcement in mouse and rat models of alcohol dependence. *Neuropharmacology*,

An effort has been mounted to understand the mechanisms of alcohol dependence in a way that may allow for greater efficacy in treatment. It has long been suggested that drugs of abuse seize fundamental reward pathways and disrupt homeostasis to produce compulsive drug seeking behaviors. Ghrelin, an endogenous hormone that affects hunger state and release of growth hormone, has been shown to increased alcohol intake following administration, while antagonists decrease intake. Using rodent models of dependence, the current study examined the effects of two ghrelin receptor antagonists, [DLys3]-GHRP-6 (DLys) and JMV2959, on dependence-induced alcohol self-administration. In two experiments adult male C57BL/6J mice and Wistar rats were made dependent via intermittent ethanol vapor exposure. In another experiment, adult male C57BL/6J mice were made dependent using the intragastric alcohol consumption (IGAC) procedure. Ghrelin receptor antagonists were given prior to voluntary ethanol drinking. Ghrelin antagonists reduced ethanol intake, preference, and operant self-administration of ethanol and sucrose across these models, but did not decrease food consumption in mice. In experiments 1 and 2, voluntary drinking was reduced by ghrelin receptor antagonists, however this reduction did not persist across days. Despite the transient effects to ghrelin antagonists, the drugs had renewed effectiveness following a break in administration as seen in experiment 1. The results show the ghrelin system as a potential target for studies of alcohol abuse. Further research is needed to determine the central mechanisms of these drugs and their influence on addiction in order to design effective pharmacotherapies.

Gonzalez-Otero, D. M., Ruiz de Gauna, S., Ruiz, J., Daya, M., Wik, L., Russell, J. K., et al. (2015). Chest compression rate feedback based on transthoracic impedance. *Resuscitation*,

BACKGROUND: Quality of cardiopulmonary resuscitation (CPR) is an important determinant of

survival from cardiac arrest. The use of feedback devices is encouraged by current resuscitation guidelines as it helps rescuers to improve quality of CPR performance. AIM: To determine the feasibility of a generic algorithm for feedback related to chest compression (CC) rate using the transthoracic impedance (TTI) signal recorded through the defibrillation pads. METHODS: We analysed 180 episodes collected equally from three different emergency services, each one using a unique defibrillator model. The new algorithm computed the CC-rate every 2s by analysing the TTI signal in the frequency domain. The obtained CC-rate values were compared with the gold standard, computed using the compression force or the ECG and TTI signals when the force was not recorded. The accuracy of the CC-rate, the proportion of alarms of inadequate CC-rate, chest compression fraction (CCF) and the mean CC-rate per episode were calculated. RESULTS: Intervals with CCs were detected with a mean sensitivity and a mean positive predictive value per episode of 96.3% and 97.0%, respectively. Estimated CC-rate had an error below 10% in 95.8% of the time. Mean percentage of accurate alarms per episode was 98.2%. No statistical differences were found between the gold standard and the estimated values for any of the computed metrics. CONCLUSION: We developed an accurate algorithm to calculate and provide feedback on CC-rate using the TTI signal. This could be integrated into automated external defibrillators and help improve the quality of CPR in basic-life-support settings.

Gross, S. M., & Rotwein, P. (2015). Akt signaling dynamics in individual cells. *Journal of Cell Science*,

The protein kinase Akt is a key intracellular mediator of many biological processes, yet knowledge of Akt signaling dynamics is limited. Here we have constructed a fluorescent reporter molecule in a lentiviral delivery system to assess Akt kinase activity at the single cell level. The reporter, a fusion between a modified FoxO1 transcription factor and clover, a green fluorescent protein, rapidly translocates from the nucleus to the cytoplasm in response to Akt stimulation. Because of its long half-life and the intensity of clover fluorescence, the sensor provides a robust readout that can be tracked for days under a range of biological conditions. Using this reporter, we find that stimulation of Akt activity by IGF-I is encoded into stable and reproducible analog responses at the population level, but that single cell signaling outcomes are variable. This reporter, which provides a simple and dynamic measure of Akt activity, should be compatible with many cell

types and experimental platforms, and thus opens the door to new insights into how Akt regulates its biological responses.

Güç, E., Fankhauser, M., Lund, A. W., Swartz, M. A., & Kilarski, W. W. (2014). Long-term intravital immunofluorescence imaging of tissue matrix components with epifluorescence and two-photon microscopy. *Journal of Visualized Experiments : JoVE*, (86)

Besides being a physical scaffold to maintain tissue morphology, the extracellular matrix (ECM) is actively involved in regulating cell and tissue function during development and organ homeostasis. It does so by acting via biochemical, biomechanical, and biophysical signaling pathways, such as through the release of bioactive ECM protein fragments, regulating tissue tension, and providing pathways for cell migration. The extracellular matrix of the tumor microenvironment undergoes substantial remodeling, characterized by the degradation, deposition and organization of fibrillar and non-fibrillar matrix proteins. Stromal stiffening of the tumor microenvironment can promote tumor growth and invasion, and cause remodeling of blood and lymphatic vessels. Live imaging of matrix proteins, however, to this point is limited to fibrillar collagens that can be detected by second harmonic generation using multi-photon microscopy, leaving the majority of matrix components largely invisible. Here we describe procedures for tumor inoculation in the thin dorsal ear skin, immunolabeling of extracellular matrix proteins and intravital imaging of the exposed tissue in live mice using epifluorescence and two-photon microscopy. Our intravital imaging method allows for the direct detection of both fibrillar and non-fibrillar matrix proteins in the context of a growing dermal tumor. We show examples of vessel remodeling caused by local matrix contraction. We also found that fibrillar matrix of the tumor detected with the second harmonic generation is spatially distinct from newly deposited matrix components such as tenascin C. We also showed long-term (12 hours) imaging of T-cell interaction with tumor cells and tumor cells migration along the collagen IV of basement membrane. Taken together, this method uniquely allows for the simultaneous detection of tumor cells, their physical microenvironment and the endogenous tissue immune response over time, which may provide important insights into the mechanisms underlying tumor progression and ultimate success or resistance to therapy.

Guo, L., Chen, Z., Amarnath, V., Yancey, P. G., Van Lenten, B. J., Savage, J. R., et al. (2015). Isolevuglandin-type lipid aldehydes induce the inflammatory response of macrophages by modifying phosphatidylethanolamines and activating the receptor for advanced glycation endproducts. *Antioxidants and Redox Signaling, 22*(18), 1633-1645.

Aims: Increased lipid peroxidation occurs in many conditions associated with inflammation. Because lipid peroxidation produces lipid aldehydes that can induce inflammatory responses through unknown mechanisms, elucidating these mechanisms may lead to development of better treatments for inflammatory diseases. We recently demonstrated that exposure of cultured cells to lipid aldehydes such as isolevuglandins (IsoLG) results in the modification of phosphatidylethanolamine (PE). We therefore sought to determine (i) whether PE modification by isolevuglandins (IsoLG-PE) occurred in vivo, (ii) whether IsoLG-PE stimulated the inflammatory responses of macrophages, and (iii) the identity of receptors mediating the inflammatory effects of IsoLG-PE. Results: IsoLG-PE levels were elevated in plasma of patients with familial hypercholesterolemia and in the livers of mice fed a high-fat diet to induce obesity and hepatosteatosis. IsoLG-PE potently stimulated nuclear factor kappa B (NFκB) activation and expression of inflammatory cytokines in macrophages. The effects of IsoLG-PE were blocked by the soluble form of the receptor for advanced glycation endproducts (sRAGE) and by RAGE antagonists. Furthermore, macrophages derived from the bone marrow of Ager null mice failed to express inflammatory cytokines in response to IsoLG-PE to the same extent as macrophages from wild-type mice. Innovation: These studies are the first to identify IsoLG-PE as a mediator of macrophage activation and a specific receptor, RAGE, which mediates its biological effects. Conclusion: PE modification by IsoLG forms RAGE ligands that activate macrophages, so that the increased IsoLG-PE generated by high circulating cholesterol levels or high-fat diet may play a role in the inflammation associated with these conditions. Antioxid. Redox Signal. 22, 1633-1645.

Haendel, M. A., Vasilevsky, N., Brush, M., Hochheiser, H. S., Jacobsen, J., Oellrich, A., et al. (2015). Disease insights through cross-species phenotype comparisons. *Mammalian Genome : Official Journal of the International Mammalian Genome Society,*

New sequencing technologies have ushered in a new era for diagnosis and discovery of new

causative mutations for rare diseases. However, the sheer numbers of candidate variants that require interpretation in an exome or genomic analysis are still a challenging prospect. A powerful approach is the comparison of the patient's set of phenotypes (phenotypic profile) to known phenotypic profiles caused by mutations in orthologous genes associated with these variants. The most abundant source of relevant data for this task is available through the efforts of the Mouse Genome Informatics group and the International Mouse Phenotyping Consortium. In this review, we highlight the challenges in comparing human clinical phenotypes with mouse phenotypes and some of the solutions that have been developed by members of the Monarch Initiative. These tools allow the identification of mouse models for known disease-gene associations that may otherwise have been overlooked as well as candidate genes may be prioritized for novel associations. The culmination of these efforts is the Exomiser software package that allows clinical researchers to analyse patient exomes in the context of variant frequency and predicted pathogenicity as well the phenotypic similarity of the patient to any given candidate orthologous gene.

Hagler, S., Jimison, H. B., Bajcsy, R., & Pavel, M. (2014). Quantification of human movement for assessment in automated exercise coaching. *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014,* pp. 5836-5839.
Quantification of human movement is a challenge in many areas, ranging from physical therapy to robotics. We quantify of human movement for the purpose of providing automated exercise coaching in the home. We developed a model-based assessment and inference process that combines biomechanical constraints with movement assessment based on the Microsoft Kinect camera. To illustrate the approach, we quantify the performance of a simple squatting exercise using two model-based metrics that are related to strength and endurance, and provide an estimate of the strength and energy-expenditure of each exercise session. We look at data for 5 subjects, and show that for some subjects the metrics indicate a trend consistent with improved exercise performance.

Hakki, M., Rattray, R. M., & Press, R. D. (2015). The clinical impact of coronavirus infection in patients with hematologic malignancies and hematopoietic stem cell transplant recipients. *Journal of*

Clinical Virology : The Official Publication of the Pan American Society for Clinical Virology, *68*, 1-5.

BACKGROUND: Compared to other respiratory viruses, relatively little is known about the clinical impact of coronavirus (CoV) infection after hematopoietic stem cell transplant (HSCT) or in patients with hematologic malignancies. OBJECTIVES: To characterize the role of CoV in respiratory tract infections among HSCT and hematologic malignancy patients. STUDY DESIGN: We conducted a retrospective review of all cases of CoV infection documented by polymerase chain reaction, (PCR)-based testing on nasopharyngeal and bronchoalveolar lavage fluid samples between June 2010 and 2013. Cases of CoV infection occurring in HSCT and hematologic malignancy patients were identified and the clinical characteristics of these cases were compared to other respiratory viruses. RESULTS: CoV was identified in 2.6% (n=43) of all samples analyzed (n=1661) and in 6.8% of all samples testing positive for a respiratory virus (n=631). 33 of 38 (86.8%) of patients in whom CoV was identified were HSCT and hematologic malignancy patients. Among these patients, CoV was detected in 9.7% of unique infection episodes, with only rhinovirus/enterovirus (RhV/EnV) infection being more common. Group I CoV subtypes accounted for 76.3% of cases, and 57% of infections were diagnosed between December and March. CoV infection was associated with upper respiratory tract symptoms in most patients, similar to other respiratory viruses. Possible and proven lower respiratory tract disease was less common compared to other respiratory viruses except RhV/EnV. CONCLUSIONS: CoV is frequently detected in HSCT and hematologic malignancy patients in whom suspicion for a respiratory viral infection exists, but is less likely to progress to lower respiratory tract disease than most other respiratory viruses.

Hansen, L., Leo, M. C., Chang, M. F., Zaman, A., Naugler, W., & Schwartz, J. (2015). Symptom distress in patients with end-stage liver disease toward the end of life. *Gastroenterology Nursing : The Official Journal of the Society of Gastroenterology Nurses and Associates*, *38*(3), 201-210.

Research on symptom distress experienced by patients with end-stage liver disease at the end of life is limited. The aims of the study were to describe presence, frequency, severity, and distress of symptoms in patients with end-stage liver disease toward the end of life and to describe the variability in psychological and physical symptom distress between and within patients over time.

This study used a prospective, longitudinal descriptive design. Data were collected from 20 patients once a month for up to 6 months. Participants completed the Memorial Symptom Assessment Scale, which reports a total score, a Global Distress Index score, and a psychological and a physical distress score. Patients reported lack of energy, pain, difficulty sleeping, and feeling drowsy as the most frequent, severe, and distressing symptoms. Global Distress Index mean scores (measured on a 1-4 scale) ranged from 2.6 to 2.9 across time. There was notable variability in psychological and physical distress scores between and within patients across time. Gaining knowledge about the prevalent symptoms experienced by patients with end-stage liver disease and the trajectory of these symptoms is crucial for designing interventions that optimize well-being in patients with end-stage liver disease as they are approaching death.

Harris, M. A., Freeman, K. A., & Duke, D. C. (2015). Seeing is believing: Using skype to improve diabetes outcomes in youth. *Diabetes Care*,

OBJECTIVE: The objective of this study was to compare the relative effectiveness of two modes of delivering Behavioral Family Systems Therapy-Diabetes (BFST-D) to improve adherence and glycemic control among adolescents with type 1 diabetes with suboptimal glycemic control (HbA1c >/=9.0% [74.9 mmol/mol]): face to face in clinic (clinic) and Internet videoconferencing (Skype) conditions. RESEARCH DESIGN AND METHODS: Adolescents ages 12 to 18 years and at least one adult caregiver were randomized to receive BFST-D via the clinic or Skype condition. Participants completed up to 10 therapy sessions within a 12-week period. Changes in youth- and parent-reported adherence and glycemic control were compared before and after the intervention and at follow-up assessment. RESULTS: Using an intent-to-treat analytic approach, no significant between-group differences were identified between the before, after, and follow-up assessments. Groups were collapsed to examine the overall effects of BFST-D on adherence and glycemic control. Results identified that statistically significant improvements in adherence and glycemic control occurred from before to after the intervention; improvements were maintained at 3-month follow-up. CONCLUSIONS: Delivery of BFST-D via Internet-based videoconferencing is viable for addressing nonadherence and suboptimal glycemic control in adolescents with type 1 diabetes, potentially reducing important barriers to care for youth and families.

Hart, R. A., Marshall, L. M., Hiratzka, S. L., Kane, M. S., Volpi, J., & Hiratzka, J. R. (2014). Functional limitations due to stiffness as a collateral impact of instrumented arthrodesis of the lumbar spine. *Spine*, *39*(24), E1468-E1474.

STUDY DESIGN.: Prospective cohort study. OBJECTIVE.: To understand whether patients actually perceive increased limitations as compared with their preoperative state due to stiffness after lumbar arthrodesis. SUMMARY OF BACKGROUND DATA.: Lumbar arthrodesis by intention eliminates spinal motion in an attempt to decrease pain, deformity, and instability. Independent of pain, loss of mobility can impact ability to perform certain activities of daily living. The lumbar stiffness disability index (LSDI) is a validated measure of the effect of lumbar stiffness on functional activities. To date, no prospective evaluations of stiffness impacts on patient function after lumbar arthrodesis have been reported. METHODS.: The LSDI, 36-Item Short Form Health Survey, and Oswestry Disability Index were administered preoperatively and at 2-year minimum follow-up to 62 adult patients undergoing lumbar fusion for degenerative disease or spinal deformity. Patients also completed a satisfaction questionnaire at 2 years. Patients were separated according to the number of lumbar arthrodesis levels. Pre- and postoperative LSDI, 36-Item Short Form Health Survey physical composite score, and Oswestry Disability Index scores were compared using paired t tests. RESULTS.: Significant improvements in Oswestry Disability Index were observed across all arthrodesis levels, and significant improvements in physical composite score were observed at level 1 and at 5 or more levels. Patients undergoing 1-level arthrodesis demonstrated statistically significant decreases in LSDI scores, indicating less impact from stiffness than at baseline. Patients with 3 or 4 levels and 5 or more levels of arthrodesis showed increases in LSDI scores, although none reached significance with the numbers available. Forty-six percent of patients reported that low back stiffness created significant limitations in activities of daily living, although 97% indicated that they would undergo the same procedure again and 91% reported that any increase in stiffness was an acceptable trade-off for their functional improvements from lumbar arthrodesis. CONCLUSION.: Patients undergoing elective lumbar arthrodesis reported relatively limited functional deficit due to stiffness at 2-year follow-up. Paradoxically, patients undergoing 1-level arthrodesis actually reported significantly less limitation due to stiffness postoperatively. Although the effects of stiffness did trend toward greater impacts among patients undergoing longer fusions, 91% of

patients were satisfied with trade-offs of function and pain relief in exchange for perceived increases in lumbar stiffness.Level of Evidence: 2. Copyright © 2014 Lippincott Williams & Wilkins.

Hasegawa, K., Bittner, J. C., Nonas, S. A., Stoll, S. J., Watase, T., Gabriel, S., et al. (2015). Children and adults with frequent hospitalizations for asthma exacerbation, 2012-2013: A multicenter observational study. *The Journal of Allergy and Clinical Immunology.in Practice*, BACKGROUND: Earlier studies reported that many patients were frequently hospitalized for asthma exacerbation. However, there have been no recent multicenter studies to characterize this patient population with high morbidity and health care utilization. OBJECTIVE: To examine the proportion and characteristics of children and adults with frequent hospitalizations for asthma exacerbation. METHODS: A multicenter chart review study of patients aged 2 to 54 years who were hospitalized for asthma exacerbation at 1 of 25 hospitals across 18 US states during the period 2012 to 2013 was carried out. The primary outcome was frequency of hospitalizations for asthma exacerbation in the past year (including the index hospitalization). RESULTS: The cohort included 369 children (aged 2-17 years) and 555 adults (aged 18-54 years) hospitalized for asthma exacerbation. Over the 12-month period, 36% of the children and 42% of the adults had 2 or more (frequent) hospitalizations for asthma exacerbation. Among patients with frequent hospitalizations, guideline-recommended outpatient management was suboptimal. For example, among adults, 32% were not on inhaled corticosteroids at the time of index hospitalization and 75% had no evidence of a previous evaluation by an asthma specialist. At hospital discharge, among adults with frequent hospitalizations who had used no controller medications previously, 37% were not prescribed inhaled corticosteroids. Likewise, during a 3-month postdischarge period, 64% of the adults with frequent hospitalizations were not referred to an asthma specialist. Although the proportion of patients who did not receive these guideline-recommended outpatient care appeared higher in adults, these preventive measures were still underutilized in children; for example, 38% of the children with frequent hospitalizations were not referred to asthma specialist after the index hospitalization. CONCLUSIONS: This multicenter study of US patients hospitalized with asthma exacerbation demonstrated a disturbingly high proportion of

patients with frequent hospitalizations and ongoing evidence of suboptimal longitudinal asthma care.

Hechler, T., Kanstrup, M., Holley, A. L., Simons, L. E., Wicksell, R., Hirschfeld, G., et al. (2015). Systematic review on intensive interdisciplinary pain treatment of children with chronic pain. *Pediatrics*,

BACKGROUND AND OBJECTIVE: Pediatric debilitating chronic pain is a severe health problem, often requiring complex interventions such as intensive interdisciplinary pain treatment (IIPT). Research is lacking regarding the effectiveness of IIPT for children. The objective was to systematically review studies evaluating the effects of IIPT. METHODS: Cochrane, Medline/Ovid, PsycInfo/OVID, PubMed, PubPsych, and Web of Science were searched. Studies were included if (1) treatment was coordinated by >/=3 health professionals, (2) treatment occurred within an inpatient/day hospital setting, (3) patients were /=10 participants at posttreatment. The child's pain condition, characteristics of the IIPT, and 5 outcome domains (pain intensity, disability, school functioning, anxiety, depressive symptoms) were extracted at baseline, posttreatment, and follow-up. RESULTS: One randomized controlled trial and 9 nonrandomized treatment studies were identified and a meta-analysis was conducted separately on pain intensity, disability, and depressive symptoms revealing positive treatment effects. At posttreatment, there were large improvements for disability, and small to moderate improvements for pain intensity and depressive symptoms. The positive effects were maintained at short-term follow-up. Findings demonstrated extreme heterogeneity. CONCLUSIONS: Effects in nonrandomized treatment studies cannot be attributed to IIPT alone. Because of substantial heterogeneity in measures for school functioning and anxiety, meta-analyses could not be computed. There is preliminary evidence for positive treatment effects of IIPT, but the small number of studies and their methodological weaknesses suggest a need for more research on IIPTs for children.

Henry, J. A., Griest, S., Thielman, E., McMillan, G., Kaelin, C., & Carlson, K. F. (2015). Tinnitus functional index: Development, validation, outcomes research, and clinical application. *Hearing Research*,

The Tinnitus Research Consortium (TRC) issued a Request for Proposals in 2003 to develop a new

tinnitus outcome measure that would: (1) be highly sensitive to treatment effects (validated for "responsiveness"); (2) address all major dimensions of tinnitus impact; and (3) be validated for scaling the negative impact of tinnitus. A grant was received by M. Meikle to conduct the study. In that observational study, all of the TRC objectives were met, with the final 25-item Tinnitus Functional Index (TFI) containing eight subscales. The study was published in 2012, and since then the TFI has received increasing international use and is being translated into at least 14 languages. The present study utilized data from a randomized controlled trial (RCT) that involved testing the efficacy of "tinnitus telephone education" as intervention for bothersome tinnitus. These data were used to confirm results from the original TFI study. Overall, the TFI performed well in the RCT with Cohen's d being 1.23. There were large differences between the eight different subscales, ranging from a mean 13.2-point reduction (for the Auditory subscale) to a mean 26.7-point reduction (for the Relaxation subscale). Comparison of TFI performance was made with the Tinnitus Handicap Inventory. All of the results confirmed sensitivity of the TFI along with its subscales. This article is part of a Special Issue entitled .

Heppner, K. M., Marks, S., Holland, J., Ottaway, N., Smiley, D., Dimarchi, R., et al. (2015). Contribution of brown adipose tissue activity to the control of energy balance by GLP-1 receptor signalling in mice. *Diabetologia*,

Aims/hypothesis: We assessed the contribution of glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) signalling to thermogenesis induced by high-fat diet (HFD) consumption. Furthermore, we determined whether brown adipose tissue (BAT) activity contributes to weight loss induced by chronic subcutaneous treatment with the GLP-1R agonist, liraglutide, in a model of diet-induced obesity. Methods: Metabolic phenotyping was performed using indirect calorimetry in wild-type (WT) and Glp1r-knockout (KO) mice during chow and HFD feeding at room temperature and at thermoneutrality. In a separate study, we investigated the contribution of BAT thermogenic capacity to the weight lowering effect induced by GLP-1 mimetics by administering liraglutide (10 or 30 nmol kg−1 day−1 s.c.) to diet-induced obese (DIO) mice for 6 or 4 weeks, respectively. In both studies, animals were subjected to a noradrenaline (norepinephrine)-stimulated oxygen consumption (Formula presented.) test. Results: At thermoneutrality, HFD-fed Glp1r-KO mice had similar energy expenditure (EE) compared with HFD-fed WT controls. However, HFD-fed

Glp1r-KO mice exhibited relatively less EE when housed at a cooler standard room temperature, and had relatively lower (Formula presented.) in response to a noradrenaline challenge, which is consistent with impaired BAT thermogenic capacity. In contrast to the loss of function model, chronic peripheral liraglutide treatment did not increase BAT activity as determined by noradrenaline-stimulated (Formula presented.) and BAT gene expression. Conclusions/interpretation: These data suggest that although endogenous GLP-1R signalling contributes to increased BAT thermogenesis, this mechanism does not play a significant role in the food intake-independent body weight lowering effect of the GLP-1 mimetic liraglutide in DIO mice. © 2015 Springer-Verlag Berlin Heidelberg

Hh, D., N, M., M, G., M, B., A, S., O, Y., et al. (2015). Social markers of mild cognitive impairment: Proportion of word counts in free conversational speech. *Current Alzheimer Research*, BACKGROUND: Detecting early signs of Alzheimer's disease (AD) and mild cognitive impairment (MCI) during the pre-symptomatic phaseis becoming increasingly important for cost-effective clinical trials and also for deriving maximum benefit from currently available treatment strategies. However, distinguishing early signs of MCI from normal cognitive aging is difficult. Biomarkers have been extensively examined as early indicators of the pathological process for AD, but assessing these biomarkers is expensive and challenging to apply widely among pre-symptomatic community dwelling older adults. Here we propose assessment of social markers, which could provide an alternative or complementary and ecologically valid strategy for identifyingthe pre-symptomatic phase leading to MCI and AD Methods: The data came from a larger randomized controlled clinical trial (RCT), where we examined whether daily conversational interactions using remote video telecommunications software could improve cognitive functions of older adult participants. We assessed the proportion of words generated by participants out of total words produced by both participants and staff interviewers using transcribed conversations during the intervention trial as an indicator of how two people (participants and interviewers) interact with each other in one-on-one conversations. We examined whether the proportion differed between those with intact cognition and MCI, using first, generalized estimating equations with the proportion as outcome, and second, logistic regression models with cognitive status as outcome in order to estimate the area under ROC curve (ROC AUC). RESULTS: Compared to those with

normal cognitive function, MCI participants generated a greater proportion of words out of the total number of words during the timed conversation sessions (p=0.01). This difference remained after controlling for participant age, gender, interviewer and time of assessment (p=0.03).The logistic regression models showed the ROC AUC of identifying MCI (vs. normals) was 0.71 (95% Confidence Interval: 0.54 - 0.89) when average proportion of word counts spoken by subjects was included univariately into the model. CONCLUSIONS: An ecologically valid social marker such as the proportion of spoken words produced during spontaneous conversations may be sensitive to transitions from normal cognition to MCI.

Hill, A. P., van Santen, J., Gorman, K., Langhorst, B. H., & Fombonne, E. (2015). Memory in language-impaired children with and without autism. *Journal of Neurodevelopmental Disorders*, *7*(1), 19-015-9111-z. Epub 2015 Jun 14.

BACKGROUND: A subgroup of young children with autism spectrum disorders (ASD) have significant language impairments (phonology, grammar, vocabulary), although such impairments are not considered to be core symptoms of and are not unique to ASD. Children with specific language impairment (SLI) display similar impairments in language. Given evidence for phenotypic and possibly etiologic overlap between SLI and ASD, it has been suggested that language-impaired children with ASD (ASD + language impairment, ALI) may be characterized as having both ASD and SLI. However, the extent to which the language phenotypes in SLI and ALI can be viewed as similar or different depends in part upon the age of the individuals studied. The purpose of the current study is to examine differences in memory abilities, specifically those that are key "markers" of heritable SLI, among young school-age children with SLI, ALI, and ALN (ASD + language normal). METHODS: In this cross-sectional study, three groups of children between ages 5 and 8 years participated: SLI (n = 18), ALI (n = 22), and ALN (n = 20). A battery of cognitive, language, and ASD assessments was administered as well as a nonword repetition (NWR) test and measures of verbal memory, visual memory, and processing speed. RESULTS: NWR difficulties were more severe in SLI than in ALI, with the largest effect sizes in response to nonwords with the shortest syllable lengths. Among children with ASD, NWR difficulties were not associated with the presence of impairments in multiple ASD domains, as reported previously. Verbal memory difficulties were present in both SLI and ALI groups relative

to children with ALN. Performance on measures related to verbal but not visual memory or processing speed were significantly associated with the relative degree of language impairment in children with ASD, supporting the role of verbal memory difficulties in language impairments among early school-age children with ASD. CONCLUSIONS: The primary difference between children with SLI and ALI was in NWR performance, particularly in repeating two- and three-syllable nonwords, suggesting that shared difficulties in early language learning found in previous studies do not necessarily reflect the same underlying mechanisms.

Hinson, A. M., Kandil, E., O'Brien, S., Spencer, H. J., Hohmann, S. F., & Stack, B. C.,Jr. (2015). Trends in robotic thyroid surgery in the united states from 2009 through 2013. *Thyroid : Official Journal of the American Thyroid Association*,

BACKGROUND: The objective of this study was to describe national trends in robotic thyroid surgery from 2009 through 2013. METHODS: The University HealthSystem Consortium (UHC) database was searched for patients undergoing robotic thyroidectomy (RT) from 2009 through 2013. Another US institution's RT data, not included in the UHC database, were also evaluated. Patient demographics, institutional volume, comorbid conditions, complications, and cost information were analyzed. RESULTS: Sixty-one institutions performed 484 RT during the study period. From 2009 through 2011, US annual RT volume increased from 39 cases to 140. Annual volume dropped to 69 cases in 2012 and 93 cases in 2013. Higher volume centers reported lower complication rates ($P<0.02$). Hematoma formation (3.7%) was the most common complication, and there was one death. Over ten percent of patients were obese. Brachial plexus injury and axillary skin flap perforations were reported in less than one percent of cases. Mean cost for a total RT was $13,287 ($5,125 - $42,444). CONCLUSIONS: From 2009 through early 2011, there was a steady increase in RT volume, especially among high volume institutions. In mid to late 2011, there was a noticeable drop in RT volume, which significantly altered the projected trajectory of the procedure in this country. Despite higher complication rates, lower volume centers perform the majority of RT and are also responsible for recent increases in RT utilization patterns in the US.

Home, P. D., Bergenstal, R. M., Bolli, G. B., Ziemen, M., Rojeski, M., Espinasse, M., et al. (2015). New insulin glargine 300 Units/mL versus glargine 100 Units/mL in people with type 1 diabetes: A randomized, phase 3a, open-label clinical trial (EDITION 4). *Diabetes Care*,
OBJECTIVE: Insulin therapy in type 1 diabetes still provides suboptimal outcomes. Insulin glargine 300 units/mL (Gla-300), with a flatter pharmacodynamic profile compared with insulin glargine 100 units/mL (Gla-100), is an approach to this problem. RESEARCH DESIGN AND METHODS: People with type 1 diabetes, using a mealtime and basal insulin regimen, were randomized open-label to Gla-300 or Gla-100 and to morning or evening injection, continuing the mealtime analog, and followed up for 6 months. RESULTS: Participants (n = 549) were a mean age of 47 years, had a duration of diabetes of 21 years, and a BMI of 27.6 kg/m2. The change in HbA1c (primary end point; baseline 8.1%) was equivalent in the two treatment-groups (difference, 0.04% [95% CI -0.10 to 0.19]) (0.4 mmol/mol [-1.1 to 2.1]), and Gla-300 was thus noninferior. Similar results with wider 95% CIs were found for morning and evening injection times and for prebreakfast self-measured plasma glucose (SMPG) overall. Results were also similar for Gla-300 when morning and evening injection time was compared, including overlapping 8-point SMPG profiles. Hypoglycemia did not differ, except for the first 8 weeks of the study, when nocturnal confirmed or severe hypoglycemia was lower with Gla-300 (risk ratio 0.69 [95% CI 0.53-0.91]). Hypoglycemia with Gla-300 did not differ by time of injection. The basal insulin dose was somewhat higher at 6 months for Gla-300. The adverse event profile did not differ and was independent of the Gla-300 time of injection. Weight gain was lower with Gla-300. CONCLUSIONS: In long-duration type 1 diabetes, Gla-300 provides similar glucose control to Gla-100, with a lower risk of hypoglycemia after transfer from other insulins, independent of time of injection, and less weight gain.

Hornick, N. I., Huan, J., Doron, B., Goloviznina, N. A., Lapidus, J., Chang, B. H., et al. (2015). Serum exosome MicroRNA as a minimally-invasive early biomarker of AML. *Scientific Reports*, *5*, 11295.
Relapse remains the major cause of mortality for patients with Acute Myeloid Leukemia (AML). Improved tracking of minimal residual disease (MRD) holds the promise of timely treatment adjustments to preempt relapse. Current surveillance techniques detect circulating blasts that coincide with advanced disease and poorly reflect MRD during early relapse. Here, we investigate

exosomes as a minimally invasive platform for a microRNA (miRNA) biomarker. We identify a set of miRNA enriched in AML exosomes and track levels of circulating exosome miRNA that distinguish leukemic xenografts from both non-engrafted and human CD34+ controls. We develop biostatistical models that reveal circulating exosomal miRNA at low marrow tumor burden and before circulating blasts can be detected. Remarkably, both leukemic blasts and marrow stroma contribute to serum exosome miRNA. We propose development of serum exosome miRNA as a platform for a novel, sensitive compartment biomarker for prospective tracking and early detection of AML recurrence.

Howieson, D. B., Mattek, N., Dodge, H. H., Erten-Lyons, D., Zitzelberger, T., & Kaye, J. A. (2015). Memory complaints in older adults: Prognostic value and stability in reporting over time. *SAGE Open Medicine, 3*, 10.1177/2050312115574796.

OBJECTIVE: The purpose of this longitudinal study was to examine the prognostic value of subjective memory complaints in 156 cognitively intact community-dwelling older adults with a mean age of 83 years. METHODS: Participants were assessed for subjective memory complaints, cognitive performance, functional status, and mood at annual evaluations with a mean follow-up of 4.5 years. RESULTS: Subjective memory complaint at entry (n=24) was not associated with impaired memory performance and did not predict memory decline or progression to incipient dementia. Memory complaints were inconsistent across examinations for 62% of participants who reported memory problems. CONCLUSIONS: Memory complaints by older adults are inconsistent over time. Memory complaint's value as a research criterion for selecting people at risk for dementia is weak among community dwelling older adults. Age, length of follow-up, and other population characteristics may affect the implication of self-reported memory problems.

Huan, J., Hornick, N. I., Goloviznina, N. A., Kamimae-Lanning, A. N., David, L. L., Wilmarth, P. A., et al. (2015). Coordinate regulation of residual bone marrow function by paracrine trafficking of AML exosomes. *Leukemia,*

We recently demonstrated that acute myeloid leukemia (AML) cell lines and patient-derived blasts release exosomes that carry RNA and protein; following in vitro transfer, AML exosomes produce proangiogenic changes in bystander cells. We reasoned that paracrine exosome

trafficking may have a broader role in shaping the leukemic niche. In a series of in vitro studies and murine xenografts, we demonstrate that AML exosomes downregulate critical retention factors (Scf, Cxcl12) in stromal cells, leading to hematopoietic stem and progenitor cell (HSPC) mobilization from the bone marrow. Exosome trafficking also regulates HSPC directly, and we demonstrate declining clonogenicity, loss of CXCR4 and c-Kit expression, and the consistent repression of several hematopoietic transcription factors, including c-Myb, Cebp-beta and Hoxa-9. Additional experiments using a model of extramedullary AML or direct intrafemoral injection of purified exosomes reveal that the erosion of HSPC function can occur independent of direct cell-cell contact with leukemia cells. Finally, using a novel multiplex proteomics technique, we identified candidate pathways involved in the direct exosome-mediated modulation of HSPC function. In aggregate, this work suggests that AML exosomes participate in the suppression of residual hematopoietic function that precedes widespread leukemic invasion of the bone marrow direct and indirectly via stromal components.Leukemia accepted article preview online, 25 June 2015. doi:10.1038/leu.2015.163.

Huertas-Vazquez, A., Nelson, C. P., Sinsheimer, J. S., Reinier, K., Uy-Evanado, A., Teodorescu, C., et al. (2015). Cumulative effects of common genetic variants on risk of sudden cardiac death. *IJC Heart and Vasculature, 7*, 88-91.

Background: Genome-wide association studies and candidate-gene based approaches have identified multiple common variants associated with increased risk of sudden cardiac death (SCD). However, the independent contribution of these individual loci to disease risk is modest. Objective: To investigate the cumulative effects of genetic variants previously associated with SCD risk. Methods: A total of 966 SCD cases from the Oregon-Sudden Unexpected Death Study and 1926 coronary artery disease controls from the Wellcome Trust Case-Control Consortium were investigated. We generated genetic risk scores (GRSs) for each trait composed of variants previously associated with SCD or with abnormalities in specific electrocardiographic traits such as QRS duration, QTc interval and heart rate. GRSs were calculated using a weighted approach based on the number of risk alleles weighted by the beta coefficients derived from the original studies. We also compared the highest and lowest quintiles for the GRS composed of SCD SNPs. Results: Increased cumulative risk was observed for a GRS composed of 14 SCD-SNPs (OR. =

1.17 [1.05-1.29], P. = 0.002). The risk for SCD was 1.5 fold greater in the highest risk quintile when compared to the lowest risk quintile (OR. = 1.46 [1.11-1.92]). We did not observe significant associations with SCD for SNPs that determine electrocardiographic traits. Conclusions: A modest but significant effect on SCD risk was identified for a GRS composed of 14 previously associated SCD SNPs. While next generation sequencing methodology will continue to identify additional novel variants, these findings represent proof of concept for the additive effects of gene variants on SCD risk. © 2015 The Authors. Published by Elsevier Ireland Ltd.

Huguet, N., McFarland, B. H., & Kaplan, M. S. (2015). A comparison of suicides and undetermined deaths by poisoning among women: An analysis of the national violent death reporting system. *Archives of Suicide Research*, *19*(2), 190-201.

The study compared the prevalence of common suicide risk factors between poisoning deaths classified as injuries of undetermined intent or suicides among women. Data were derived from the 2003–10 National Violent Death Reporting System. Multiple logistic regression assessed the factors associated with 799 undetermined deaths (relative to 3,233 suicides). Female decedents with lower education, a substance use problem, and a health problem were more likely to be classified as undetermined death. Older women, those with an intimate partner problem, financial problem, depressed mood, mental health problem, attempted suicide, and disclosed intent to die were less likely to be classified as undetermined death. The present study raises the possibility that many (perhaps most) undetermined female poisoning deaths are suicides. © 2015 International Academy for Suicide Research.

Hutfless, S., Abramson, O., Heyman, M. B., Bayless, T. M., Li, D. K., Winthrop, K., et al. (2015). Infections requiring hospitalization as predictors of pediatric-onset crohn's disease and ulcerative colitis. *Gastroenterology Research and Practice*, *2015*, 690581.

Objectives. To assess the relationship between infections and the risk of pediatric-onset inflammatory bowel disease (IBD). Methods. We conducted a nested case-control study of 501 incident cases aged </=17 years and 9,442 controls who were members of Kaiser Permanente Northern California for at least one consecutive year between 1996 and 2006. IBD was confirmed and the incidence date was adjudicated by pediatric gastroenterologists. Hospitalized infections

were identified from the principal diagnosis code of electronic inpatient records. Medications to treat infections were identified during the hospitalization. Conditional logistic regression was used to assess the associations between hospitalized infections, medications, and Crohn's disease and ulcerative colitis. Results. In the year prior to diagnosis, both hospitalized infection of any system (OR 6.3; 95% CI 1.6-23.9) and hospitalized intestinal infection (OR 19.4; 95% CI 2.6-143.2) were associated with CD. Hospitalized infections of any system were inversely associated with UC after excluding the year prior to diagnosis (OR 0.4; 95% CI 0.2-0.9). No UC case had a hospitalized gastrointestinal infection prior to diagnosis. Conclusion. Infections appear to play opposite roles prior to the diagnosis of CD and UC. Infections may be associated with an increased risk of CD and a decreased risk of UC.

Iancu, O. D., Colville, A., Oberbeck, D., Darakjian, P., McWeeney, S. K., & Hitzemann, R. (2015). Cosplicing network analysis of mammalian brain RNA-seq data utilizing WGCNA and mantel correlations. *Frontiers in Genetics*, *6*, 174.

Across species and tissues and especially in the mammalian brain, production of gene isoforms is widespread. While gene expression coordination has been previously described as a scale-free coexpression network, the properties of transcriptome-wide isoform production coordination have been less studied. Here we evaluate the system-level properties of cosplicing in mouse, macaque, and human brain gene expression data using a novel network inference procedure. Genes are represented as vectors/lists of exon counts and distance measures sensitive to exon inclusion rates quantifies differences across samples. For all gene pairs, distance matrices are correlated across samples, resulting in cosplicing or cotranscriptional network matrices. We show that networks including cosplicing information are scale-free and distinct from coexpression. In the networks capturing cosplicing we find a set of novel hubs with unique characteristics distinguishing them from coexpression hubs: heavy representation in neurobiological functional pathways, strong overlap with markers of neurons and neuroglia, long coding lengths, and high number of both exons and annotated transcripts. Further, the cosplicing hubs are enriched in genes associated with autism spectrum disorders. Cosplicing hub homologs across eukaryotes show dramatically increasing intronic lengths but stable coding region lengths. Shared transcription factor binding sites increase coexpression but not cosplicing; the reverse is true for

splicing-factor binding sites. Genes with protein-protein interactions have strong coexpression and cosplicing. Additional factors affecting the networks include shared microRNA binding sites, spatial colocalization within the striatum, and sharing a chromosomal folding domain. Cosplicing network patterns remain relatively stable across species.

Immanuel, S. A., Kohler, M., Kabir, M. M., Saint, D. A., & Baumert, M. (2014). Symbolic dynamics of respiratory cycle related sleep EEG in children with sleep disordered breathing. *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014*, pp. 6016-6019.

Childhood sleep disordered breathing (SDB) is characterized by an increased work of breathing, restless night sleep and excessive daytime sleepiness and has been associated with cognitive impairment, behavioral disturbances and early cardiovascular changes. Compared to normal controls, children with SDB have elevated arousal thresholds and their sleep EEG may elicit cortical activation associated with arousals but often too subtle to be visually scored. The aim of this study was to assess EEG complexity throughout the respiratory cycle based on symbolic dynamics in children with SDB (n=40) and matched healthy controls. EEG amplitude values were symbolized based on the quartiles of their distribution and words of length 3 were formed and classed into 4 types based on their patterns. Children with SDB showed less complex EEG dynamics in non-REM sleep that was unrelated to the respiratory phase. In REM sleep normal children showed a respiratory phase-related reduction in EEG variability during the expiratory phase compared to inspiration, which was not apparent in children with SDB. In conclusion, respiratory cycle related EEG dynamics are altered in children with SDB during REM sleep and indicate changes in cortical activity.

Iwahori, S., Hakki, M., Chou, S., & Kalejta, R. F. (2015). Molecular determinants for the inactivation of the retinoblastoma tumor suppressor by the viral cyclin-dependent kinase UL97. *The Journal of Biological Chemistry*,

The retinoblastoma (Rb) tumor suppressor restricts cell cycle progression by repressing E2F-responsive transcription. Cellular cyclin-dependent kinase (CDK)-mediated Rb inactivation through phosphorylation disrupts Rb-E2F complexes, stimulating transcription. The human

cytomegalovirus (HCMV) UL97 protein is a viral CDK (v-CDK) that phosphorylates Rb. Here we show that UL97 phosphorylates 11 of the 16 consensus CDK sites in Rb. A cleft within Rb accommodates peptides with the amino acid sequence LxCxE. UL97 contains three such motifs. We determined that the first LxCxE motif (L1) of UL97 and the Rb cleft enhance UL97-mediated Rb phosphorylation. A UL97 mutant with a non-functional L1 motif (UL97-L1m) displays significantly reduced Rb phosphorylation at multiple sites. Curiously, however, it efficiently disrupts Rb-E2F complexes but fails to relieve Rb-mediated repression of E2F reporter constructs. The HCMV immediate early 1 (IE1) protein cooperates with UL97-L1m to inactivate Rb in transfection assays, likely indicating that cells infected with a UL97-L1m mutant virus show no defects in growth or E2F-responsive gene expression because of redundant viral mechanisms to inactivate Rb. Our data suggest that UL97 possesses a mechanism to elicit E2F-dependent gene expression distinct from disruption of Rb-E2F complexes and dependent upon both the L1 motif of UL97 and the cleft region of Rb.

Jacobs, P. G., Wan, E. A., Schafermeyer, E., Adenwala, F., Paul, A. S., Preiser, N., et al. (2014). Measuring in-home walking speed using wall-mounted RF transceiver arrays. *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014*, pp. 914-917.

In this paper we present a new method for passively measuring walking speed using a small array of radio transceivers positioned on the walls of a hallway within a home. As a person walks between a radio transmitter and a receiver, the received signal strength (RSS) detected by the receiver changes in a repeatable pattern that may be used to estimate walking speed without the need for the person to wear any monitoring device. The transceivers are arranged as an array of 4 with a known distance between the array elements. Walking past the first pair of transceivers will cause a peak followed by a second peak when the person passes the second pair of transceivers. The time difference between these peaks is used to estimate walking speed directly. We further show that it is possible to estimate the walking speed by correlating the shape of the signal using a single pair of transceivers positioned across from each other in a hallway or doorframe. RMSE performance was less than 15 cm/s using a 2-element array, and less than 8 cm/s using a 4-element array relative to a gait mat used for ground truth.

Jacques, S. L. (2015). Probing nanoscale tissue structure using light scattering. *Novel Techniques in Microscopy*, *NTM 2015*,

Light scattering by a tissue encodes the size distribution and granularity of the scattering structures in the tissue. (1) Goniometry shows how the angle of photon deflection depends on the structure size. (2) Diffuse light measurements shows that the wavelength dependence of the reduced scattering coefficient governing diffuse light propagation is dependent on the size distribution of scatterers in a tissue. (3) Confocal reflectance is sensitive to the anisotropy of light scattering, which depends on the size distribution of scatterers. (4) Narrowangle planar backscatter of collimated incident white light from a tissue yields a spectrum that encodes the spatial frequency of refractive index fluctuations in the tissue, i.e., the granularity of the tissue. Light scattering is a useful tool for characterizing the nanoscale structure of tissues. © OSA 2015.

Jamal, S. A., Arampatzis, S., Harrison, S. L., Bucur, R. C., Ensrud, K., Orwoll, E. S., et al. (2014). Hyponatremia and fractures: Findings from the MrOS study. *Journal of Bone and Mineral Research*, *30*(6), 970-975.

Hyponatremia may be a risk factor for fracture. To determine the relationship between hyponatremia and fracture we conducted cross-sectional and longitudinal analyses using data from the Osteoporotic Fractures in Men (MrOS) study. The MrOS study enrolled 5122 community dwelling men aged ≥65 years from six centers across the United States. We excluded men taking bisphosphonates, those with unknown medication history, those without serum sodium measures, or those with out of range assays for serum sodium. Serum sodium was measured at study entry. Subjects were followed for fractures (nonspine [including hip], hip, incident morphometric, and prevalent morphometric) for up to 9 years. We used Cox proportional hazards models to analyze the association between serum sodium levels (<135 mmol/L versus ≥135 mmol/L) and risk of nonspine and hip fractures, with results presented as hazard ratios (HRs) and 95% confidence intervals (CIs). We examined the association between morphometric vertebral fractures and serum sodium using logistic regression models, presented as odds ratios (ORs) and 95% CI. Hyponatremia was observed in 64 men (1.2% of the cohort). After adjusting for age, BMI, study center, and other covariates, we found that, compared to men with serum sodium ≥135 mmol/L, those with serum sodium <135 mmol/L, had an increased risk of hip

fracture (HR = 3.04; 95% CI, 1.37 to 6.75), prevalent morphometric spine fracture (OR = 2.46; 95% CI, 1.22 to 4.95), and incident morphometric spine fracture (OR = 3.53; 95% CI, 1.35 to 9.19), but not nonspine fracture (OR = 1.44; 95% CI, 0.85 to 2.44). Adjusting for bone mineral density (BMD) did not change our findings. Our data show that hyponatremia is associated with up to a doubling in the risk of hip and morphometric spine fractures, independent of BMD. Further studies, to determine how hyponatremia causes fractures and if correction of hyponatremia decreases fractures, are needed. © 2014 American Society for Bone and Mineral Research. © 2015 American Society for Bone and Mineral Research.

Jayaram, H., Abegao Pinto, L., Prokosch, V., Matlach, J., Skonieczna, K., Mercieca, K., et al. (2015). Circadian arterial blood pressure variation and glaucoma progression: More questions than answers? *American Journal of Hypertension*,

Jensen, E. T., Shah, N. D., Hoffman, K., Sonnenberg, A., Genta, R. M., & Dellon, E. S. (2015). Seasonal variation in detection of oesophageal eosinophilia and eosinophilic oesophagitis. *Alimentary Pharmacology & Therapeutics*,

BACKGROUND: Seasonal variation has been reported in diagnosis of eosinophilic oesophagitis (EoE), but results are not consistent across studies and there are no national-level data in the USA. AIM: To determine if there is seasonal variation in diagnosis of oesophageal eosinophilia and EoE in the USA, while accounting for factors such as climate zone and geographic variation. METHODS: This was a cross-sectional study using a USA national pathology database. Patients with oesophageal eosinophilia (>/=15 eosinophils per high-power field) comprised the primary case definition and were compared to those with normal oesophageal biopsies. We calculated the crude and adjusted odds of oesophageal eosinophilia by season, as well as by day of the year. Sensitivity analyses were performed using more restrictive case definitions of EoE, and after stratification by climate zone. RESULTS: Exactly, 14 524 cases with oesophageal eosinophilia and 90 459 normal controls were analysed. The adjusted odds of oesophageal eosinophilia were higher in the late spring and summer months, with the highest odds in July (aOR: 1.13; 95% CI: 1.03-1.24). These findings persisted with increasing levels of oesophageal eosinophilia, as well as across EoE case definitions. Seasonal variation was strongest in temperate and cold climates, and

peak diagnosis varied by climate zone. CONCLUSIONS: There is a mild but consistent seasonal variation in the diagnosis of oesophageal eosinophilia and EoE, with cases more frequently diagnosed during summer months. These findings take into account climate and geographic differences, suggesting that aeroallergens may contribute to disease development or flare.

Jensen, J. T., Hanna, C., Yao, S., Bauer, C., Morgan, T. K., & Slayden, O. D. (2015). Characterization of tubal occlusion after transcervical polidocanol foam (PF) infusion in baboons. *Contraception*, OBJECTIVE: Our long-term goal is to develop a nonsurgical method of fallopian tubal occlusion for the purpose of permanent contraception. We have previously demonstrated that transcervical administration of 5% polidocanol foam (PF) can create tubal occlusion in macaques but that multiple treatments are required. In this study, we assessed the efficacy of various regimens of PF with and without depomedroxyprogesterone acetate (DMPA) (to control ovarian cycle phase) in the baboon. STUDY DESIGN: Adult cycling female baboons were evaluated for tubal patency by hysterosalpingography and then received a transcervical infusion of PF with (+) or without (-) an intramuscular injection of DMPA (3.5 mg/kg). Two concentrations of PF were compared: 1% [(+) DMPA, n=5; (-) DMPA, n=3] and 5% [(+) DMPA, n=4; (-) DMPA, n=3]. Controls received (+) DMPA (n=2) or (-) DMPA, (n=3) only. The reproductive tracts were removed 1-3 months after treatment for examination. RESULTS: No fallopian tubal occlusion was observed in negative controls (+/-DMPA). Histologic complete tubal occlusion was observed in 3/8 of females treated with 1% PF and in 6/7 treated with 5% PF. Histologic evaluation suggested that 1% PF is associated with prolonged chronic inflammation (more than 2-3 months), while 5% treatment eliminates the epithelial lining, at least focally, and resolves into complete occlusion within 1-2 months. This pattern of complete occlusion was seen in all 4 females that received 5% PF (+DMPA) and in 2/3 that received 5% PF (-DMPA). CONCLUSION: In a baboon model of transcervical permanent contraception, a single treatment with 5% PF resulted in complete tubal occlusion more reliably (85%) than 1% PF (38%). Cotreatment with DMPA may improve treatment results with 5% PF but requires additional study. IMPLICATIONS: A finding that a single transcervical treatment with 5% PF can occlude the fallopian tubes of baboon supports further study of this approach as a novel strategy for permanent contraception for women.

Johnson, A. L., Blaine, E. T., & Lewis, A. D. (2015). Renal pigmentation due to chronic bismuth administration in a rhesus macaque (macaca mulatta). *Veterinary Pathology*, *52*(3), 576-579.
Renal pigmentation due to the administration of exogenous compounds is an uncommon finding in most species. This report describes renal pigmentation and intranuclear inclusions of the proximal convoluted tubules due to chronic bismuth administration in a rhesus macaque. An 11-year-old Indian-origin rhesus macaque with a medical history of chronic intermittent vomiting had been treated with bismuth subsalicylate, famotidine, and omeprazole singly or in combination over the course of 8 years. At necropsy, the renal cortices were diffusely dark green to black. Light and electron microscopy revealed intranuclear inclusions within the majority of renal proximal tubular epithelial cells. These inclusions appeared magenta to brown when stained with hematoxylin and eosin and were negative by the Ziehl-Neelsen acid-fast stain. Elemental analysis performed on frozen kidney measured bismuth levels to be markedly elevated at 110.6 ppm, approximately 500 to 1000 times acceptable limits. To our knowledge, this is the first report of renal bismuth deposition in a rhesus macaque resulting in renal pigmentation and intranuclear inclusions. © The Author(s) 2014.

Johnson, R. C., Weinberg, O. K., Cascio, M. J., Dahl, G. V., Mitton, B. A., Silverman, L. B., et al. (2015). Cytogenetic variation of B-lymphoblastic leukemia with intrachromosomal amplification of chromosome 21 (iAMP21): A multi-institutional series review. *American Journal of Clinical Pathology*, *144*(1), 103-112.
OBJECTIVES: B-lymphoblastic leukemia (B-ALL) with intrachromosomal amplification of chromosome 21 (iAMP21) is a relatively uncommon manifestation of acute leukemia and limited predominantly to the pediatric population. Case-specific information regarding flow cytometric, morphologic, and laboratory findings of this subtype of leukemia is currently lacking. METHODS: We searched the databases of three large institutions for lymphoblastic leukemia with iAMP21 from 2005 through 2012 and analyzed the clinicopathologic features. RESULTS: We identified 17 cases with five or more RUNX1 signals on interphase nuclei, 14 of which were consistent with the Children's Oncology Group (COG) definition for iAMP21-namely, the presence of three or more RUNX1 signals on one marker chromosome. These cases showed a statistically significant lower peripheral WBC count and older age at diagnosis compared with all pediatric cases of B-ALL. We

also identified three cases with increased RUNX1 signals scattered on multiple marker chromosomes that did not meet the COG definition of iAMP21 but showed similar 21q instability and older age at presentation. CONCLUSIONS: Our findings not only demonstrate that B-ALL with iAMP21 is truly a distinct clinicopathologic entity but also suggest that a subset of cases of B-ALL with iAMP21 can show variable cytogenetic features.

Kabir, M. M., Immanuel, S. A., Tafreshi, R., Saint, D. A., & Baumert, M. (2014). Effect of resistive inspiratory and expiratory loading on cardio-respiratory interaction in healthy subjects. *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014,* pp. 710-713.

Resistive loading affects the breathing pattern and causes an increase in negative intrathoracic pressure. The aim of this paper was to study the influence inspiratory and expiratory loading on cardio-respiratory interaction. We recorded electrocardiogram (ECG) and respiratory inductance plethysmogram (RIP) in 11 healthy male subjects under normal and resistive loading conditions. The R-R time series were extracted from the ECG and respiratory phases were calculated from the ribcage and abdominal RIP using the Hilbert transform. Both the series were transformed into ternary symbol vectors based on the changes between two successive R-R intervals or respiratory phases, respectively. Subsequently, words of length '3 digits' were formed and the correspondence between words of the two series was determined to quantify cardio-respiratory interaction. Adding inspiratory and expiratory resistive loads resulted in an increase in inspiratory and expiatory time, respectively. Furthermore, we observed a significant increase in cardio-respiratory interaction during inspiratory resistive loading as compared to expiratory resistive loading (ribcage: 22.1±7.2 vs. 12.5±4.3 %, $p<0.0001$; abdomen: 18.8±8.5 vs. 12.1±3.1 %, $p<0.05$, respectively). Further studies may aid in better understanding the underlying physiological mechanisms and management of patients with breathing disorders.

Kaneshiro, B., & Edelman, A. (2014). *Adolescents who are obese* Springer New York.

Recent estimates place the prevalence of obesity in adolescent women at approximately 18 %. Thus, providing contraception for adolescents and young women who are obese represents an increasingly common clinical scenario. Unfortunately, there is little research regarding hormonal

contraceptive efficacy in obese adult women and almost no research which includes adolescents. While all contraceptives appear to be safe in obese teens, studies of hormonal contraceptives in adults suggest efficacy may be slightly impaired with increasing weight for the combined oral contraceptive pill and the transdermal contraceptive patch. Most contraceptives are not associated with weight gain; however, there may be a subset of adolescents who are susceptible to weight gain with depot medroxyprogesterone acetate (DMPA).

Karasawa, T., & Steyger, P. S. (2015). An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. *Toxicology Letters*,

Cisplatin is one of the most widely-used drugs to treat cancers. However, its nephrotoxic and ototoxic side-effects remain major clinical limitations. Recent studies have improved our understanding of the molecular mechanisms of cisplatin-induced nephrotoxicity and ototoxicity. While cisplatin binding to DNA is the major cytotoxic mechanism in proliferating (cancer) cells, nephrotoxicity and ototoxicity appear to result from toxic levels of reactive oxygen species and protein dysregulation within various cellular compartments. In this review, we discuss molecular mechanisms of cisplatin-induced nephrotoxicity and ototoxicity. We also discuss potential clinical strategies to prevent nephrotoxicity and ototoxicity and their current limitations.

Karoly, H. C., Bryan, A. D., Weiland, B. J., Mayer, A., Dodd, A., & Feldstein Ewing, S. W. (2015). Does incentive-elicited nucleus accumbens activation differ by substance of abuse? an examination with adolescents. *Developmental Cognitive Neuroscience*,

Numerous questions surround the nature of reward processing in the developing adolescent brain, particularly in regard to polysubstance use. We therefore sought to examine incentive-elicited brain activation in the context of three common substances of abuse (cannabis, tobacco, and alcohol). Due to the role of the nucleus accumbens (NAcc) in incentive processing, we compared activation in this region during anticipation of reward and loss using a monetary incentive delay (MID) task. Adolescents (ages 14-18; 66% male) were matched on age, gender, and frequency of use of any common substances within six distinct groups: cannabis-only (n=14), tobacco-only (n=34), alcohol-only (n=12), cannabis+tobacco (n=17),

cannabis+tobacco+alcohol (n=17), and non-using controls (n=38). All groups showed comparable behavioral performance on the MID task. The tobacco-only group showed decreased bilateral nucleus accumbens (NAcc) activation during reward anticipation as compared to the alcohol-only group, the control group, and both polysubstance groups. Interestingly, no differences emerged between the cannabis-only group and any of the other groups. Results from this study suggest that youth who tend toward single-substance tobacco use may possess behavioral and/or neurobiological characteristics that differentiate them from both their substance-using and non-substance-using peers.

Katzman, W. B., Harrison, S. L., Fink, H. A., Marshall, L. M., Orwoll, E., Barrett-Connor, E., et al. (2015). Physical function in older men with hyperkyphosis. *The Journals of Gerontology.Series A, Biological Sciences and Medical Sciences, 70*(5), 635-640.

BACKGROUND: Age-related hyperkyphosis has been associated with poor physical function and is a well-established predictor of adverse health outcomes in older women, but its impact on health in older men is less well understood. METHODS: We conducted a cross-sectional study to evaluate the association of hyperkyphosis and physical function in 2,363 men, aged 71-98 (M = 79) from the Osteoporotic Fractures in Men Study. Kyphosis was measured using the Rancho Bernardo Study block method. Measurements of grip strength and lower extremity function, including gait speed over 6 m, narrow walk (measure of dynamic balance), repeated chair stands ability and time, and lower extremity power (Nottingham Power Rig) were included separately as primary outcomes. We investigated associations of kyphosis and each outcome in age-adjusted and multivariable linear or logistic regression models, controlling for age, clinic, education, race, bone mineral density, height, weight, diabetes, and physical activity. RESULTS: In multivariate linear regression, we observed a dose-related response of worse scores on each lower extremity physical function test as number of blocks increased, p for trend /=4 blocks, 20% (N = 469) of men were characterized with hyperkyphosis. In multivariate logistic regression, men with hyperkyphosis had increased odds (range 1.5-1.8) of being in the worst quartile of performing lower extremity physical function tasks ($p < .001$ for each outcome). Kyphosis was not associated with grip strength in any multivariate analysis. CONCLUSIONS: Hyperkyphosis is

associated with impaired lower extremity physical function in older men. Further studies are needed to determine the direction of causality.

Kelley, K. A., Crawford, J. D., Thomas, K., Gardiner, S. K., & Johnson, N. G. (2015). A comparison of breast-specific gamma imaging of invasive lobular carcinomas and ductal carcinomas. *JAMA Surgery*,

Kelly, M. J., & Rønnekleiv, O. K. (2015). Minireview: Neural signaling of estradiol in the hypothalamus. *Molecular Endocrinology*, *29*(5), 645-657.

Klein, E. (2015). Eloquent brain, ethical challenges: Functional brain mapping in neurosurgery. *Seminars in Ultrasound, CT and MRI*,
Functional brain mapping is an increasingly relied upon tool in presurgical planning and intraoperative decision making. Mapping allows personalization of structure-function relationships when surgical or other treatment of pathology puts eloquent functioning like language or vision at risk. As an innovative technology, functional brain mapping holds great promise but also raises important ethical questions. In this article, recent work in neuroethics on functional imaging and functional neurosurgery is explored and applied to functional brain mapping. Specific topics discussed in this article are incidental findings, responsible innovation, and informed consent. © 2015 Elsevier Inc.

Klein, E. P. (2014). Patient health incentives: Ethical challenges and frameworks. *International Journal of Behavioral Medicine*, *21*(6), 995-1004.
BACKGROUND: Patient incentives for encouraging healthy behavior raise a number of ethical concerns: Do they target the vulnerable? Do they involve psychological manipulation? Do they undermine intrinsic motivation? PURPOSE: To the purpose of this paper is to provide an overview of ethical challenges raised by patient incentives and incentive programs and develop a systematic approach to understanding and analyzing these ethical challenges. METHOD: Ethical considerations raised by patient incentives can be broadly grouped into two kinds: medical ("patient-oriented") and public health ("constituent-oriented") concerns. Ethical frameworks suitable to these kinds of concerns are explored. RESULTS: Two ethical frameworks are applied

to the challenges raised by patient incentives: (1) Incentives are assessed in terms of personal and social responsibility for health; and (2) incentives are assessed as elements of normatively structured clinical relationships (e.g., the traditional patient-clinician relationship). CONCLUSION: A better understanding of ethical concerns and the resources available within the personal responsibility and clinical encounter frameworks suggest complementary guidance may be available for approaching many of the ethical issues raised by patient incentives.

Klufas, M. A., Patel, S. N., Ryan, M. C., Gupta, M. P., Jonas, K. E., Ostmo, S., et al. (2015). Influence of fluorescein angiography on the diagnosis and management of retinopathy of prematurity. *Ophthalmology*,

PURPOSE: To examine the influence of fluorescein angiography (FA) on the diagnosis and management of retinopathy of prematurity (ROP). DESIGN: Prospective cohort study. PARTICIPANTS: Nine recognized ROP experts (3 pediatric ophthalmologists and 6 retina specialists) interpreted 32 sets (16 color fundus photographs and 16 color fundus photographs paired with the corresponding FA images) of wide-angle retinal images from infants with ROP. METHODS: All experts independently reviewed the 32 image sets on a secure website and provided a diagnosis and management plan for the case presented, first based on color fundus photographs alone, and then based on color fundus photographs and corresponding FA images. MAIN OUTCOME MEASURES: Sensitivity and specificity of the ROP diagnosis (zone, stage, plus disease, and category, i.e., no ROP, mild ROP, type 2 ROP, and ROP requiring treatment) were calculated using a consensus reference standard diagnosis, determined from the diagnosis of the color fundus photographs by 3 experienced readers in combination with the clinical diagnosis based on ophthalmoscopic examination. The kappa statistic was used to analyze the average intergrader agreement among experts for the diagnosis of zone, stage, plus disease, and category. RESULTS: Addition of FA to color fundus photography resulted in a significant improvement in sensitivity for diagnosis of stage 3 or worse disease (39.8% vs. 74.1%; P = 0.008), type 2 or worse ROP (69.4% vs. 86.8%; P = 0.013), and pre-plus or worse disease (50.5 vs. 62.6%; P = 0.031). There was a nonsignificant trend toward improved sensitivity for diagnosis of ROP requiring treatment (22.2% vs. 40.3%; P = 0.063). Using the kappa statistic, addition of FA to color fundus photography significantly improved intergrader agreement for

diagnosis of ROP requiring treatment. Addition of FA to color fundus photography did not affect intergrader agreement significantly for the diagnosis of stage, zone, or plus disease. CONCLUSIONS: Compared with color fundus photography alone, FA may improve the sensitivity of diagnosis of ROP by experts, particularly for stage 3 disease. In addition, intergrader agreement for diagnosis of ROP requiring treatment may improve with FA interpretation.

Ko, A. L., Lee, A., Raslan, A. M., Ozpinar, A., McCartney, S., & Burchiel, K. J. (2015). Trigeminal neuralgia without neurovascular compression presents earlier than trigeminal neuralgia with neurovascular compression. *Journal of Neurosurgery*, , 1-9.

OBJECT Trigeminal neuralgia (TN) occurs and recurs in the absence of neurovascular compression (NVC). To characterize what may be distinct patient populations, the authors examined age at onset in patients with TN with and without NVC. METHODS A retrospective review of patients undergoing posterior fossa surgery for Type I TN at Oregon Health & Science University from 2009 to 2013 was undertaken. Charts were reviewed, and imaging and operative data were collected for patients with and without NVC. Mean, median, and the empirical cumulative distribution of onset age were determined. Statistical analysis was performed using Student t-test, Wilcoxon and Kolmogorov-Smirnoff tests, and Kaplan-Meier analysis. Multivariate analysis was performed using a Cox proportional hazards model. RESULTS The charts of 219 patients with TN were reviewed. There were 156 patients who underwent posterior fossa exploration and microvascular decompression or internal neurolysis: 129 patients with NVC and 27 without NVC. Mean age at symptoms onset for patients with and without NVC was 51.1 and 42.6 years, respectively. This difference (8.4 years) was significant (t-test: $p = 0.007$), with sufficient power to detect an effect size of 8.2 years. Median age between groups with and without NVC was 53.25 and 41.2 years, respectively ($p = 0.003$). Histogram analysis revealed a bimodal age at onset in patients without NVC, and cumulative distribution of age at onset revealed an earlier presentation of symptoms ($p = 0.003$) in patients without NVC. Chi-square analysis revealed a trend toward female predominance in patients without NVC, which was not significant ($p = 0.08$). Multivariate analysis revealed that age at onset was related to NVC but not sex, symptom side or distribution, or patient response to medical treatment. CONCLUSIONS NVC is neither sufficient nor necessary for the development of TN. Patients with TN without NVC may represent a distinct

population of younger, predominantly female patients. Further research into the pathophysiology underlying this debilitating disease is needed.

Ko, J. W., Lorzano, A., & Mirarchi, A. J. (2015). Effectiveness of a microvascular surgery training curriculum for orthopaedic surgery residents. *The Journal of Bone and Joint Surgery.American Volume*, *97*(11), 950-955.

BACKGROUND: The safe and effective acquisition of microvascular surgical skills is a challenge for any residency program. Variable clinical exposure to microsurgery, premiums on operating room efficiency, and a steep learning curve make these skills difficult to acquire through clinical experience alone. The purpose of this study was to determine the effectiveness of a training curriculum on the development of microvascular surgical skills in our orthopaedic residents. METHODS: A microvascular training curriculum was completed during each third-year resident's rotation on the hand and upper-extremity service. The training cycle began with learning the basics of microvascular surgery on nonliving models and progressed to performing end-to-end arterial anastomoses on a live rat femoral artery in the second session. Outcome evaluations consisted of the Global Rating Scale score, achievement of patency, and time to completion. T test analyses of Global Rating Scale scores, achievement of patency, and time to completion were conducted to determine significance ($p < 0.05$). RESULTS: All residents significantly improved ($p < 0.005$) on Global Rating Scale scores from a mean score (and standard deviation) of 15 +/- 4 points for the initial score to 20 +/- 3 points for the post-test score. Of the twelve residents, patency was achieved by eleven at the final evaluation, compared with six before training. Time to completion of the anastomosis also significantly improved ($p < 0.005$), from a mean of 37:17 +/- 8:41 minutes for the initial time to 24:46 +/- 5:32 minutes for the final time. CONCLUSIONS: In an effort to improve the microvascular surgical skills of orthopaedic residents at our institution, a microvascular training curriculum was developed and was implemented. This curriculum was effective at improving resident microvascular surgical skills at the completion of an eight-week course.

Kopplin, L. J., & Mansberger, S. L. (2015). Predictive value of screening tests for visually significant eye disease. *American Journal of Ophthalmology*,

PURPOSE: To determine the predictive value of ophthalmic screening tests with visually significant eye disease in a cohort of American Indian/Alaskan Natives from the Pacific Northwest. DESIGN: Validity assessment of a possible screening protocol. METHODS: Ophthalmic technicians performed a screening examination including medical and ocular history, best-corrected visual acuity, limbal anterior chamber depth assessment, frequency doubling technology perimetry (FDT, C-20-5), confocal scanning laser ophthalmoscopy, nonmydriatic digital photography, and tonometry on 429 participants. An ophthalmologist performed a comprehensive eye exam on subjects with one or more abnormal screening tests and a random selection of those with normal screening tests. We used univariate and multivariate logistic regression to determine the association between abnormal screening test results and visually significant eye disease. We also determined the predictive value of screening tests with ocular disease. RESULTS: Univariate analysis identified history of eye disease or diabetes mellitus ($p<.001$), visual acuity <20/40 ($p<.001$), abnormal/poor quality confocal scanning laser ophthalmoscopy ($p<.001$), abnormal FDT ($p<.001$), and abnormal/poor quality non-mydriatic imaging ($p<.001$) as associated with visually significant eye disease. A multivariate analysis found visually significant eye disease to be associated ($p<.001$; receiver operating curve area= .827, negative predictive value=84%) with four screening tests: visual acuity <20/40, abnormal/poor quality non-mydriatic imaging, abnormal FDT and abnormal/poor quality confocal scanning laser ophthalmoscopy. CONCLUSIONS: Ophthalmic technicians performing a subset of screening tests may provide an accurate and efficient means of screening for eye disease in an American Indian/Alaskan Native population. Confirmation of these results in other populations, particularly those with a different profile of disease prevalence is needed.

Kozar, R. A., Arbabi, S., Stein, D. M., Shackford, S. R., Barraco, R. D., Biffl, W. L., et al. (2015). Injury in the aged: Geriatric trauma care at the crossroads. *Journal of Trauma and Acute Care Surgery*, *78*(6), 1197-1209.

Kruer, R. M., Barton, C. A., Roberti, G., Gilbert, B., & McMillian, W. D. (2015). Antimicrobial prophylaxis during hirudo medicinalis therapy: A multicenter study. *Journal of Reconstructive Microsurgery*, *31*(3), 205-209.

Background Medicinal leeches (Hirudo medicinalis) are indicated for salvage of tissue flaps, grafts, or replants when venous congestion threatens tissue viability. The purpose of this study was to evaluate the efficacy of prophylactic antimicrobial agents in patients who received medicinal leech therapy. Materials and Methods A multicenter retrospective cohort study of all adult patients between January 1, 2010, and February 28, 2013, who received medicinal leech therapy was conducted. Results Antimicrobial prophylaxis was documented in 54 (91.5%) of the included patients, ciprofloxacin, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, and ceftriaxone in 33 (61.1%), 18 (33.3%), 2 (3.7%), and 2 (3.7%) patients, respectively. Surgical site infection (SSI) was found in seven (11.9%) patients, all of whom received antimicrobial prophylaxis. Aeromonas spp. was isolated in four infections, and all isolates were resistant to the chosen prophylactic agent. The SSI incidence was similar between antimicrobial prophylaxis agents. Conclusion Trimethoprim-sulfamethoxazole and ciprofloxacin appear equally effective at preventing leech-associated infections. © 2015 by Thieme Medical Publishers, Inc.

Ku, C. A., & Pennesi, M. E. (2015). Retinal gene therapy: Current progress and future prospects. *Expert Review of Ophthalmology, 10*(3), 281-299.

Clinical trials treating inherited retinal dystrophy caused by RPE65 mutations had put retinal gene therapy at the forefront of gene therapy. Both successes and limitations in these clinical trials have fueled developments in gene vectors, which continue to further advance the field. These novel gene vectors aim to more safely and efficiently transduce retinal cells, expand the gene packaging capacity of adeno-associated virus, and utilize new strategies to correct the varying mechanisms of dysfunction found with inherited retinal dystrophies. With recent clinical trials and numerous pre-clinical studies utilizing these novel vectors, the future of ocular gene therapy continues to hold vast potential. © Informa UK, Ltd.

Kuang, A., & Selden, N. R. (2014). Secondary cranial vault remodeling for restenosis after primary sagittal synostosis repair. *Pediatric Neurosurgery, 50*(2), 104-108.

The mainstay of treatment for single-suture cranial synostosis is cranial vault reconstruction. After primary cranial vault remodeling, patients are at risk for cranial restenosis and delayed intracranial hypertension, which may result in developmental delay or blindness. Synostosis

patients are therefore generally monitored periodically for signs and symptoms of intracranial hypertension that may indicate a second cranial expansion procedure. The authors present a carefully illustrated case of a patient who presented 2 years after primary cranial vault reconstruction for sagittal synostosis with a decrease in head circumference percentile, recurrent cranial dysmorphism, papilledema, headaches and computed tomographic imaging findings consistent with cranial restenosis. These findings resolved after secondary cranial vault remodeling. The authors advocate a protocol of prospective routine clinical and radiographic follow-up after primary cranial vault repair for single-suture cranial synostosis, and illustrate the specific clinical and radiographic findings suggestive of this late complication in a representative individual patient.

LaFranchi, S. H. (2015). Inaugural management guidelines for children with thyroid nodules and differentiated thyroid cancer: Children are not small adults. *Thyroid : Official Journal of the American Thyroid Association*,

Laharnar, N., Perrin, N., Hanson, G., Anger, W. K., & Glass, N. (2015). Workplace domestic violence leave laws: Implementation, use, implications. *International Journal of Workplace Health Management*, *8*(2), 109-128.

Purpose Intimate partner violence (IPV), affecting 30 percent of women worldwide, may affect employment and workplace safety. In all, 16 US states adopted laws providing leave for employed survivors. These qualitative findings are from an evaluation of Oregon's state leave law. The paper aims to discuss these issues. Design/methodology/approach The authors interviewed Oregon government employees (n=17) with past year IPV and Oregon supervisors (n=10) of past year IPV survivors. Interviews were transcribed, analyzed and coded. Findings Participants agreed that IPV has an effect on work. They reported positive workplace reactions to IPV disclosure (93 percent positive, 52 percent negative), but also negative reactions (lack of information, confidentiality, supervisor support). Several implications for supervisors were named (workload, being untrained, being a mandatory reporter, workplace safety and confidentiality). Three years after implementation, 74 percent of participants did not know the leave existed, 65 percent of survivors would have used it if known. The main barriers to usage were fear for job,

lack of payment, and stigma. The main barriers of implementation were untrained supervisors and lack of awareness. Participants (85 percent) suggested workplace training on IPV, the law and supervisor role. Practical implications Effective implementation and support of the IPV leave law is important to avoid negative consequences for survivors and the workplace. Participants called for an increase in IPV awareness and supervisor training. Originality/value These results provide important recommendations to policymakers, authorities and advocates on development, implementation and evaluation of laws adopted to support employed IPV survivors. © Emerald Group Publishing Limited.

Laidler, M. R., Thomas, A., Baumbach, J., Kirley, P. D., Meek, J., Aragon, D., et al. (2015). Statin treatment and mortality: Propensity score-matched analyses of 2007-2008 and 2009-2010 laboratory-confirmed influenza hospitalizations. *Open Forum Infectious Diseases, 2*(1), ofv028. Background. Annual influenza epidemics are responsible for substantial morbidity and mortality. The use of immunomodulatory agents such as statins to target host inflammatory responses in influenza virus infection has been suggested as an adjunct treatment, especially during pandemics, when antiviral quantities are limited or vaccine production can be delayed. Methods. We used population-based, influenza hospitalization surveillance data, propensity score-matched analysis, and Cox regression to determine whether there was an association between mortality (within 30 days of a positive influenza test) and statin treatment among hospitalized cohorts from 2 influenza seasons (October 1, 2007 to April 30, 2008 and September 1, 2009 to April 31, 2010). Results. Hazard ratios for death within the 30-day follow-up period were 0.41 (95% confidence interval [CI], .25-.68) for a matched sample from the 2007-2008 season and 0.77 (95% CI, .43-1.36) for a matched sample from the 2009 pandemic. Conclusions. The analysis suggests a protective effect against death from influenza among patients hospitalized in 2007-2008 but not during the pandemic. Sensitivity analysis indicates the findings for 2007-2008 may be influenced by unmeasured confounders. This analysis does not support using statins as an adjunct treatment for preventing death among persons hospitalized for influenza.

Lam, R. K., England, A. H., Smith, J. W., Rizzuto, A. M., Shih, O., Prendergast, D., et al. (2015). The hydration structure of dissolved carbon dioxide from X-ray absorption spectroscopy. *Chemical*

Physics Letters, *633*, 214-217.

Abstract The dissolution of carbon dioxide in water and its subsequent hydrolysis reactions comprise one of the most central processes in all of science, yet it remains incompletely understood despite enormous effort. We report the detailed characterization of dissolved CO2 gas through the combination of X-ray spectroscopy and first principles theory. The molecule acts as a hydrophobe in water with an average hydrogen bond number of 0.56. The carbon atom interacts weakly with a single water at a distance of >2.67 Å and the carbonyl oxygens serve as weak hydrogen bond acceptors, thus locally enhancing the tetrahedral water hydrogen bonding structure.

Lee, J. H., Pryce, B. A., Schweitzer, R., Ryder, M. I., & Ho, S. P. (2015). Differentiating zones at periodontal ligament-bone and periodontal ligament-cementum entheses. *Journal of Periodontal Research*,

BACKGROUND AND OBJECTIVE: The structural and functional integrity of bone-periodontal ligament (PDL)-cementum complex stems from the load-bearing attachment sites (entheses) between soft (PDL) and hard (bone, cementum) tissues. These attachment sites are responsible for the maintenance of a bone-PDL-cementum complex biomechanical function. The objective was to investigate changes in spatiotemporal expression of key biomolecules in developing and functionally active entheses. MATERIAL AND METHODS: Multilabeling technique was performed on hemimandibles of 3 wk and 3 mo-old scleraxis-GFP transgenic mice for CD146, CD31, NG2, osterix and bone sialoprotein. Regions of dominant stretch within the PDL were evaluated by identifying directionality of collagen fibrils, PDL fibroblasts and PDL cell cytoskeleton. RESULTS: CD146+ cells adjacent to CD31+ vasculature were identified at PDL-bone enthesis. NG2+ cells were located at coronal bone-PDL and apical cementum-PDL entheses in the 3-wk-old group, but at 3 mo, NG2 was positive at the entheses of the apical region and alveolar crest. NG2 and osterix were colocalized at the osteoid and cementoid regions of the PDL-bone and PDL-cementum entheses. Bone sialoprotein was prominent at the apical region of 3-wk-old mice. The directionality of collagen fibers, fibroblasts and their cytoskeleton overlapped, except in the apical region of 3 wk. CONCLUSION: Colocalization of biomolecules at zones of the PDL adjacent to attachment sites may be essential for the formation of precementum and osteoid interfaces at a

load-bearing bone-PDL-tooth fibrous joint. Biophysical cues resulting from development and function can regulate recruitment and differentiation of stem cells potentially from a vascular origin toward osteo- and cemento-blastic lineages at the PDL-bone and PDL-cementum entheses. Investigating the coupled effect of biophysical and biochemical stimuli leading to cell differentiation at the functional attachment sites is critical for developing regeneration strategies to enable functional reconstruction of the periodontal complex.

Lehmann, C. U., Longhurst, C. A., Hersh, W., Mohan, V., Levy, B. P., Embi, P. J., et al. (2015). Clinical informatics fellowship programs: In search of a viable financial model: An open letter to the centers for medicare and medicaid services. *Applied Clinical Informatics, 6*(2), 267-270.
In the US, the new subspecialty of Clinical Informatics focuses on systems-level improvements in care delivery through the use of health information technology (HIT), data analytics, clinical decision support, data visualization and related tools. Clinical informatics is one of the first subspecialties in medicine open to physicians trained in any primary specialty. Clinical Informatics benefits patients and payers such as Medicare and Medicaid through its potential to reduce errors, increase safety, reduce costs, and improve care coordination and efficiency. Even though Clinical Informatics benefits patients and payers, because GME funding from the Centers for Medicare and Medicaid Services (CMS) has not grown at the same rate as training programs, the majority of the cost of training new Clinical Informaticians is currently paid by academic health science centers, which is unsustainable. To maintain the value of HIT investments by the government and health care organizations, we must train sufficient leaders in Clinical Informatics. In the best interest of patients, payers, and the US society, it is therefore critical to find viable financial models for Clinical Informatics fellowship programs. To support the development of adequate training programs in Clinical Informatics, we request that the Centers for Medicare and Medicaid Services (CMS) issue clarifying guidance that would allow accredited ACGME institutions to bill for clinical services delivered by fellows at the fellowship program site within their primary specialty.

Lewy, A. J. (2015). Circadian rhythms and mood disorders: A guide for the perplexed. *The Journal of Clinical Psychiatry, 76*(5), e662-4.

Ozdemir and coworkers' present contribution to this journal invites the opportunity to outline some of the fundamentals concerning circadian rhythms and affective illness. Consensus or near-consensus has been reached on the tools for assessing and adjusting circadian rhythms, if not on the hypotheses for their role in seasonal affective disorder (SAD, typically winter depression), non-seasonal unipolar major depressive disorder (MDD), and bipolar disorder. First proposed in the 1980s, the dim light melatonin onset (DLMO) is now acknowledged as the most accurate biomarker for circadian phase position.

Lin, C. H., Desai, S., Nicolas, R., Gauvreau, K., Foerster, S., Sharma, A., et al. (2015). Sedation and anesthesia in pediatric and congenital cardiac catheterization: A prospective multicenter experience. *Pediatric Cardiology*,

Sedation/anesthesia is critical to cardiac catheterization in the pediatric/congenital heart patient. We sought to identify current sedation/anesthesia practices, the serious adverse event rate related to airway, sedation, or anesthesia, and the rate of intra-procedural conversion from procedural sedation to the use of assisted ventilation or an artificial airway. Data from 13,611 patients who underwent catheterization at eight institutions were prospectively collected from 2007 to 2010. Ninety-four (0.69 %) serious sedation/airway-related adverse events occurred; events were more likely to occur in smaller patients (<4 kg, OR 4.4, 95 % CI 2.3–8.2, $p < 0.001$), patients with non-cardiac comorbidities (OR 1.7, 95 % CI 1.1–26, $p < 0.01$), and patients with low mixed venous oxygen saturation (OR 2.3, 95 % CI 1.4–3.6, $p < 0.001$). Nine thousand three hundred and seventy-nine (69 %) patients were initially managed with general endotracheal anesthesia, LMA, or tracheostomy, whereas 4232 (31 %) were managed with procedural sedation without an artificial airway, of which 75 (1.77 %) patients were converted to assisted ventilation/general anesthesia. Young age (<12 months, OR 5.2, 95 % CI 2.3–11.4, $p < 0.001$), higher-risk procedure (category 4, OR 10.1, 95 % CI 6.5–15.6, $p < 0.001$), and continuous pressor/inotrope requirement (OR 11.0, 95 % CI 8.6–14.0, $p < 0.001$) were independently associated with conversion. Cardiac catheterization in pediatric/congenital patients was associated with a low rate of serious sedation/airway-related adverse events. Smaller patients with non-cardiac comorbidities or low mixed venous oxygen saturation may be at higher risk. Patients under 1 year of age, undergoing high-risk procedures, or requiring continuous

pressor/inotrope support may be at higher risk of requiring conversion from procedural sedation to assisted ventilation/general anesthesia. © 2015 Springer Science+Business Media New York

Lindauer, A., Harvath, T. A., Berry, P. H., & Wros, P. (2015). The meanings african american caregivers ascribe to dementia-related changes: The paradox of hanging on to loss. *The Gerontologist*,

PURPOSE OF THE STUDY: Using an interpretive phenomenological approach, this study explored the meaning African American (AA) caregivers ascribed to the dementia-related changes in their care-recipients. DESIGN AND METHODS: Data were gathered in this qualitative study with 22 in-depth interviews. Eleven AA caregivers for persons with dementia, living in the Pacific Northwestern United States, were interviewed twice. Four caregivers participated in an optional observation session. RESULTS: Analysis based on the hermeneutic circle revealed that, for these caregivers, the dementia-related changes meant that they had to hang on to the care-recipients for as long as possible. Caregivers recognized that the valued care-recipients were changed, but still here and worthy of respect and compassion. Ancestral family values, shaped by historical oppression, appeared to influence these meanings. IMPLICATIONS: The results from this study suggest that AA caregivers tend to focus on the aspects of the care-recipients' personalities that remain, rather than grieve the dementia-related losses. These findings have the potential to deepen gerontologists' understanding of the AA caregiver experience. This, in turn, can facilitate effective caregiver decision making and coping.

Lipin, M. Y., Taylor, W. R., & Smith, R. G. (2015). Inhibitory input to the direction selective ganglion cells is saturated at low contrast. *Journal of Neurophysiology*, , jn.00413.2015.

Direction selective ganglion cells (DSGCs) respond selectively to motion towards a "preferred" direction, but much less to motion towards the opposite "null" direction. Directional signals in the DSGC depend on GABAergic inhibition, and are observed over a wide range of speeds, which precludes motion detection based on a fixed temporal correlation. A voltage-clamp analysis, using narrow bar stimuli similar in width to the receptive field center, demonstrated that inhibition to DSGCs saturates rapidly above a threshold contrast. However, for wide bar stimuli that activate both the center and surround, inhibition depends more linearly on contrast. Excitation for both

wide and narrow bars was also more linear. We propose that positive feedback, likely within the starburst amacrine cell or its network, produces steep saturation of inhibition at relatively low contrast, which renders GABA-release essentially contrast and speed invariant, and thereby enhances the signal-to-noise ratio for direction selective signals in the spike train over a wide range of stimulus conditions. This mechanism enhances directional signals at the expense of lower sensitivity to other stimulus features such as contrast and speed. This renders GABA-release essentially contrast and speed invariant, which enhances directional signals for small objects, and thereby increases the signal-to-noise ratio for direction selective signals in the spike train over a wide range of stimulus conditions. The steep saturation of inhibition confers to a neuron immunity to noise in its spike train because when inhibition is strong, no spikes are initiated.

Liu, H. -., Banerjee, T., Guan, X., Freitas, M. A., & Parvin, J. D. (2015). The chromatin scaffold protein SAFB1 localizes SUMO-1 to the promoters of ribosomal protein genes to facilitate transcription initiation and splicing. *Nucleic Acids Research*, *43*(7), 3605-3613.

Early steps of gene expression are a composite of promoter recognition, promoter activation, RNA synthesis and RNA processing, and it is known that SUMOylation, a post-translational modification, is involved in transcription regulation. We previously found that SUMO-1 marks chromatin at the proximal promoter regions of some of the most active housekeeping genes during interphase in human cells, but the SUMOylated targets on the chromatin remained unclear. In this study, we found that SUMO-1 marks the promoters of ribosomal protein genes via modification of the Scaffold Associated Factor B (SAFB) protein, and the SUMOylated SAFB stimulated both the binding of RNA polymerase to promoters and pre-mRNA splicing. Depletion of SAFB decreased RNA polymerase II binding to promoters and nuclear processing of the mRNA, though mRNA stability was not affected. This study reveals an unexpected role of SUMO-1 and SAFB in the stimulatory coupling of promoter binding, transcription initiation and RNA processing.

Liu, Z., Dimitrov, I. E., Lenkinski, R. E., Hajibeigi, A., & Vinogradov, E. (2015). UCEPR: Ultrafast localized CEST-spectroscopy with PRESS in phantoms and in vivo. *Magnetic Resonance in*

Medicine,

PURPOSE: Chemical exchange saturation transfer (CEST) is a contrast mechanism enhancing low-concentration molecules through saturation transfer from their exchangeable protons to bulk water. Often many scans are acquired to form a Z-spectrum, making the CEST method time-consuming. Here, an ultrafast localized CEST-spectroscopy with PRESS (UCEPR) is proposed to obtain the entire Z-spectrum of a voxel using only two scans, significantly accelerating CEST. THEORY AND METHODS: The approach combines ultrafast nonlocalized CEST spectroscopy with localization using PRESS. A field gradient is applied concurrently with the saturation pulse producing simultaneous saturation of all Z-spectrum frequencies that are also spatially encoded. A readout gradient during data acquisition resolves the spatial dependence of the CEST responses into frequency. UCEPR was tested on a 3T scanner both in phantoms and in vivo. RESULTS: In phantoms, a fast Z-spectroscopy acquisition of multiple pH-variant iopamidol samples was achieved with four- to seven-fold acceleration as compared to the conventional CEST methods. In vivo, amide proton transfer (APT) in white matter of healthy human brain was measured rapidly in 48 s and with high frequency resolution (</= 0.2 ppm). CONCLUSION: Compared with conventional CEST methods, UCEPR has the advantage of rapidly acquiring high-resolution Z-spectra. Potential in vivo applications include ultrafast localized Z-spectroscopy, quantitative, or dynamic CEST studies. Magn Reson Med, 2015. (c) 2015 Wiley Periodicals, Inc.

Lo, D., Zhang, Y., Dai, M. S., Sun, X. X., Zeng, S. X., & Lu, H. (2015). Nucleostemin stabilizes ARF by inhibiting the ubiquitin ligase ULF. *Oncogene*, *34*(13), 1688-1697.

Upregulated expression of nucleolar GTPase nucleostemin (NS) has been associated with increased cellular proliferation potential and tumor malignancy during cancer development. Recent reports attribute the growth regulatory effects of NS protein to its role in facilitating ribosome production. However, the oncogenic potential of NS remains unclear, as imbalanced levels of NS have been reported to exert growth inhibitory effect by modulating p53 tumor-suppressor activity. It also remains in questions if aberrant NS levels might have a p53-independent role in regulation of cell proliferation and growth. In this study, we performed affinity purification and mass spectrometry analysis to explore protein-protein interactions influencing NS growth regulatory properties independently of p53 tumor suppressor. We

identified the alternative reading frame (ARF) protein as a key protein associating with NS and further verified the interaction through in vitro and in vivo assays. We demonstrated that NS is able to regulate cell cycle progression by regulating the stability of the ARF tumor suppressor. Furthermore, overexpression of NS suppressed ARF polyubiquitination by its E3 ligase Ubiquitin Ligase for ARF and elongated its half-life, whereas knockdown of NS led to the decrease of ARF levels. Also, we found that NS can enhance NPM stabilization of ARF. Thus, we propose that in the absence of p53, ARF can be stabilized by NS and nucleophosmin to serve as an alternative tumor-suppressor surveillance, preventing potential cellular transformation resulting from the growth-inducing effects of NS overexpression.

Longo, L. V. G., Nakayasu, E. S., Pires, J. H. S., Gazos-Lopes, F., Vallejo, M. C., Sobreira, T. J. P., et al. (2015). Characterization of lipids and proteins associated to the cell wall of the acapsular mutant cryptococcus neoformans cap 67. *Journal of Eukaryotic Microbiology*,

Cryptococcus neoformans is an opportunistic human pathogen that causes life-threatening meningitis. In this fungus, the cell wall is exceptionally not the outermost structure due to the presence of a surrounding polysaccharide capsule, which has been highly studied. Considering that there is little information about C. neoformans cell wall composition, we aimed at describing proteins and lipids extractable from this organelle, using as model the acapsular mutant C. neoformans cap 67. Purified cell wall preparations were extracted with either chloroform/methanol or hot sodium dodecyl sulfate. Total lipids fractionated in silica gel 60 were analyzed by electrospray ionization tandem mass spectrometry (ESI-MS/MS), while trypsin digested proteins were analyzed by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). We detected 25 phospholipid species among phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, and phosphatidic acid. Two glycolipid species were identified as monohexosyl ceramides. We identified 192 noncovalently linked proteins belonging to different metabolic processes. Most proteins were classified as secretory, mainly via nonclassical mechanisms, suggesting a role for extracellular vesicles (EV) in transwall transportation. In concert with that, orthologs from 86% of these proteins have previously been reported both in fungal cell wall and/or in EV. The possible role of the presently

described structures in fungal-host relationship is discussed. © 2015 International Society of Protistologists.

Lu, W., Hu, H., Sevigny, J., Gabelt, B. T., Kaufman, P. L., Johnson, E. C., et al. (2015). Rat, mouse, and primate models of chronic glaucoma show sustained elevation of extracellular ATP and altered purinergic signaling in the posterior eye. *Investigative Ophthalmology & Visual Science, 56*(5), 3075-3083.

PURPOSE: The cellular mechanisms linking elevated IOP with glaucomatous damage remain unresolved. Mechanical strains and short-term increases in IOP can trigger ATP release from retinal neurons and astrocytes, but the response to chronic IOP elevation is unknown. As excess extracellular ATP can increase inflammation and damage neurons, we asked if sustained IOP elevation was associated with a sustained increase in extracellular ATP in the posterior eye. METHODS: No ideal animal model of chronic glaucoma exists, so three different models were used. Tg-MyocY437H mice were examined at 40 weeks, while IOP was elevated in rats following injection of hypertonic saline into episcleral veins and in cynomolgus monkeys by laser photocoagulation of the trabecular meshwork. The ATP levels were measured using the luciferin-luciferase assay while levels of NTPDase1 were assessed using qPCR, immunoblots, and immunohistochemistry. RESULTS: The ATP levels were elevated in the vitreal humor of rats, mice, and primates after a sustained period of IOP elevation. The ecto-ATPase NTPDase1 was elevated in optic nerve head astrocytes exposed to extracellular ATP for an extended period. NTPDase1 was also elevated in the retinal tissue of rats, mice, and primates, and in the optic nerve of rats, with chronic elevation in IOP. CONCLUSIONS: A sustained elevation in extracellular ATP, and upregulation of NTPDase1, occurs in the posterior eye of rat, mouse, and primate models of chronic glaucoma. This suggests the elevation in extracellular ATP may be sustained in chronic glaucoma, and implies a role for altered purinergic signaling in the disease.

Lucidi, P., Porcellati, F., Yki-Jarvinen, H., Riddle, M. C., Candeloro, P., Marinelli Andreoli, A., et al. (2015). Low levels of unmodified insulin glargine in plasma of people with type 2 diabetes requiring high doses of basal insulin. *Diabetes Care, 38*(7), e96-7.

Mair, C. A., Quinones, A. R., & Pasha, M. A. (2015). Care preferences among middle-aged and older adults with chronic disease in europe: Individual health care needs and national health care infrastructure. *The Gerontologist*,

PURPOSE OF THE STUDY: The purpose of this study is to expand knowledge of care options for aging populations cross-nationally by examining key individual-level and nation-level predictors of European middle-aged and older adults' preferences for care. DESIGN AND METHODS: Drawing on data from the Survey of Health, Ageing and Retirement in Europe and the Organisation for Economic Co-operation and Development, we analyze old age care preferences of a sample of 6,469 adults aged 50 and older with chronic disease in 14 nations. Using multilevel modeling, we analyze associations between individual-level health care needs and nation-level health care infrastructure and preference for family-based (vs. state-based) personal care. RESULTS: We find that middle-aged and older adults with chronic disease whose health limits their ability to perform paid work, who did not receive personal care from informal sources, and who live in nations with generous long-term care funding are less likely to prefer family-based care and more likely to prefer state-based care. IMPLICATIONS: We discuss these findings in light of financial risks in later life and the future role of specialized health support programs, such as long-term care.

Mark, L. J., Herzer, K. R., Cover, R., Pandian, V., Bhatti, N. I., Berkow, L. C., et al. (2015). Difficult airway response team: A novel quality improvement program for managing hospital-wide airway emergencies. *Anesthesia and Analgesia*, *121*(1), 127-139.

BACKGROUND: Difficult airway cases can quickly become emergencies, increasing the risk of life-threatening complications or death. Emergency airway management outside the operating room is particularly challenging. METHODS: We developed a quality improvement program-the Difficult Airway Response Team (DART)-to improve emergency airway management outside the operating room. DART was implemented by a team of anesthesiologists, otolaryngologists, trauma surgeons, emergency medicine physicians, and risk managers in 2005 at The Johns Hopkins Hospital in Baltimore, Maryland. The DART program had 3 core components: operations, safety, and education. The operations component focused on developing a multidisciplinary difficult airway response team, standardizing the emergency response process, and deploying difficult

airway equipment carts throughout the hospital. The safety component focused on real-time monitoring of DART activations and learning from past DART events to continuously improve system-level performance. This objective entailed monitoring the paging system, reporting difficult airway events and DART activations to a Web-based registry, and using in situ simulations to identify and mitigate defects in the emergency airway management process. The educational component included development of a multispecialty difficult airway curriculum encompassing case-based lectures, simulation, and team building/communication to ensure consistency of care. Educational materials were also developed for non-DART staff and patients to inform them about the needs of patients with difficult airways and ensure continuity of care with other providers after discharge. RESULTS: Between July 2008 and June 2013, DART managed 360 adult difficult airway events comprising 8% of all code activations. Predisposing patient factors included body mass index >40, history of head and neck tumor, prior difficult intubation, cervical spine injury, airway edema, airway bleeding, and previous or current tracheostomy. Twenty-three patients (6%) required emergent surgical airways. Sixty-two patients (17%) were stabilized and transported to the operating room for definitive airway management. There were no airway management-related deaths, sentinel events, or malpractice claims in adult patients managed by DART. Five in situ simulations conducted in the first program year improved DART's teamwork, communication, and response times and increased the functionality of the difficult airway carts. Over the 5-year period, we conducted 18 airway courses, through which >200 providers were trained. CONCLUSIONS: DART is a comprehensive program for improving difficult airway management. Future studies will examine the comparative effectiveness of the DART program and evaluate how DART has impacted patient outcomes, operational efficiency, and costs of care.

Marshall, N. E., Vanderhoeven, J., Eden, K. B., Segel, S. Y., & Guise, J. -. (2015). Impact of simulation and team training on postpartum hemorrhage management in non-academic centers. *Journal of Maternal-Fetal and Neonatal Medicine, 28*(5), 495-499.

Objective: Prompt recognition and response to postpartum hemorrhage (PPH) are vital in preventing maternal morbidity and mortality. We conducted a multi-center study to evaluate in situ simulation and team training for PPH among experienced clinical teams in non-academic

hospitals in urban and rural communities. Methods: A longitudinal intervention study was performed in six Oregon community hospitals. All teams responded to an in situ simulated delivery and postpartum hemorrhage using trained actors and an obstetric birthing simulator, followed by a debriefing and training session. The simulation scenario was then repeated in 9-12months. All sessions were digitally video recorded and independently reviewed by two obstetricians using a structured evaluation form. PPH management including clinical response times were compared before and after team training using Student's paired t-test and McNemar's test. Results: Twenty-two teams completed paired case simulations. Team training significantly improved response times in the management of PPH, including the recognition of PPH, time to administer first medication, performance of uterine massage and time to administer second medication. Medical management (use of three indicated medications) improved after training from 27.3% to 63.6%, p=0.01. Conclusions: Simulation and team training significantly improved postpartum hemorrhage response times among clinically experienced community labor and delivery teams. © 2014 Informa UK Ltd.

Matte, B., Rohde, L. A., Turner, J. B., Fisher, P. W., Shen, S., Bau, C. H., et al. (2015). Reliability and validity of proposed DSM-5 ADHD symptoms in a clinical sample of adults. *The Journal of Neuropsychiatry and Clinical Neurosciences*, , appineuropsych13060137.

The DSM-5 ADHD and Disruptive Behaviors Work Group proposed two major changes for diagnosis of attention deficit hyperactivity disorder (ADHD) in adults: 1) inclusion of four new impulsivity symptoms and 2) reduction in the number of symptoms required for assigning an ADHD diagnosis. In this case-control study, the performance of these modifications was assessed in a clinical sample of 133 adult subjects (68 ADHD cases and 65 non-ADHD control subjects). The proposed new impulsivity symptoms for adults do not improve ADHD diagnosis enough to overcome potential negative effects of changing the criteria. However, fewer symptoms than the six-of-nine threshold required by DSM-IV provided the best cutoff point for identifying adults who are impaired.

Maxson, J. E., Davare, M. A., Luty, S. B., Eide, C. A., Chang, B. H., Loriaux, M. M., et al. (2015). Therapeutically targetable ALK mutations in leukemia. *Cancer Research*, *75*(11), 2146-2150.

Genome sequencing is revealing a vast mutational landscape in leukemia, offering new opportunities for treatment with targeted therapy. Here, we identify two patients with acute myelogenous leukemia and B-cell acute lymphoblastic leukemia whose tumors harbor point mutations in the ALK kinase. The mutations reside in the extracellular domain of ALK and are potently transforming in cytokine-independent cellular assays and primary mouse bone marrow colony formation studies. Strikingly, both mutations conferred sensitivity to ALK kinase inhibitors, including the FDA-approved drug crizotinib. On the basis of our results, we propose that tumors harboring ALK mutations may be therapeutically tractable for personalized treatment of certain aggressive leukemias with ALK inhibitors. Cancer Res; 75(11); 2146-50. (c)2015 AACR.

McCully, S. P., Martin, D. T., Cook, M. R., Gordon, N. T., McCully, B. H., Lee, T. H., et al. (2015). Effect of ascorbic acid concentrations on hemodynamics and inflammation following lyophilized plasma transfusion. *The Journal of Trauma and Acute Care Surgery*, *79*(1), 30-38. BACKGROUND: Compared with lyophilized plasma (LP) buffered with other acids, LP with ascorbic acid (AA) attenuates systemic inflammation and DNA damage in a combat relevant polytrauma swine model. We hypothesize that increasing concentrations of AA in transfused LP will be safe, will be hemodynamically well tolerated, and will attenuate systemic inflammation following polytraumatic injury and hemorrhage in swine. METHODS: This prospective, randomized, blinded study involved 52 female swine. Forty animals were subjected to our validated polytrauma model and resuscitated with LP. Baseline control sham (n = 6), operative control sham (n = 6), low-AA (n = 10), medium-AA (n = 10), high-AA (n = 10) groups, and a hydrochloric acid control (HCL, n = 10) were randomized. Hemodynamics, thrombelastography, and blood chemistries were assessed. Inflammatory cytokines (tumor necrosis factor alpha, interleukin 6 [IL-6], C-reactive protein, and IL-10) and DNA damage were measured at baseline, 2 hours, and 4 hours after liver injury. Significance was set at $p < 0.05$, with a Bonferroni correction for multiple comparisons. RESULTS: Hemodynamics, shock, and blood loss were similar between groups. All animals had robust procoagulant activity 2 hours following liver injury. Inflammation was similar between groups at baseline, and AA groups remained similar to HCL following liver injury. IL-6 and tumor necrosis factor alpha were increased at 2 hours and 4 hours compared with baseline within all groups ($p < 0.008$). DNA damage increased at 2 hours compared with baseline in all groups ($p <$

0.017) and further increased at 4 hours compared with baseline in HCL, low-, and high-AA groups ($p < 0.005$). C-reactive protein was similar between and within groups. IL-10 increased at 2 hours compared with baseline in low- and high-AA groups and remained elevated at 4 hours compared with baseline in the low-AA group (all, $p < 0.017$). CONCLUSION: Concentrations of AA were well tolerated and did not diminish the procoagulant activity of LP. Within our tested range of concentrations, AA can safely be used to buffer LP.

McGinley, M. J., David, S. V., & McCormick, D. A. (2015). Cortical membrane potential signature of optimal states for sensory signal detection. *Neuron*,

The neural correlates of optimal states for signal detection task performance are largely unknown. One hypothesis holds that optimal states exhibit tonically depolarized cortical neurons with enhanced spiking activity, such as occur during movement. We recorded membrane potentials of auditory cortical neurons in mice trained on a challenging tone-in-noise detection task while assessing arousal with simultaneous pupillometry and hippocampal recordings. Arousal measures accurately predicted multiple modes of membrane potential activity, including rhythmic slow oscillations at low arousal, stable hyperpolarization at intermediate arousal, and depolarization during phasic or tonic periods of hyper-arousal. Walking always occurred during hyper-arousal. Optimal signal detection behavior and sound-evoked responses, at both sub-threshold and spiking levels, occurred at intermediate arousal when pre-decision membrane potentials were stably hyperpolarized. These results reveal a cortical physiological signature of the classically observed inverted-U relationship between task performance and arousal and that optimal detection exhibits enhanced sensory-evoked responses and reduced background synaptic activity.

McLarry, J., Ferencik, M., & Shapiro, M. D. (2015). Coronary artery anomalies: A pictorial review. *Current Cardiovascular Imaging Reports*, *8*(7)

Coronary artery anomalies range in prevalence from 0.2 to 2.3 % of the population. They range from benign incidental findings to an important cause of sudden cardiac death (SCD). In fact, coronary anomalies are the second leading cause of SCD in athletes and are responsible for ~30 % of SCD in the young. Clinically, anomalous coronary arteries arising from the opposite

sinus and anomalous left coronary artery arising from the pulmonary artery are the most important as they are associated with the highest risk of mortality. Several high-risk features and their pathophysiology are reviewed. Multiple imaging modalities have been utilized to study coronary artery anomalies; however, coronary computed tomography angiography (CTA) is uniquely suited to characterize coronary artery anomalies as it allows for clear elucidation of origin, course, and termination in relationship to other relevant anatomy with high spatial resolution. This paper will provide an overview of the wide spectrum of coronary artery anomalies and variants, review the most relevant coronary CTA imaging features for each, and differentiate benign from malignant varieties. © 2015, Springer Science+Business Media New York.

Mehta, M., & Kaul, S. (2015). Reply: Handheld ultrasound is a valuble bedside tool which can supplement the bedside cardiac exam but not replace it. *JACC: Cardiovascular Imaging, 8*(5), 622.

Mehta, M., & Kaul, S. (2015). Reply: Physical examination is still necessary and important. *JACC: Cardiovascular Imaging, 8*(5), 620-621.

Mesar, T., Martin, D., Lawless, R., Podbielski, J., Cook, M., Underwood, S., et al. (2015). Human dose confirmation for self-expanding intra-abdominal foam: A translational, adaptive, multicenter trial in recently deceased human subjects. *The Journal of Trauma and Acute Care Surgery, 79*(1), 39-47.

BACKGROUND: Noncompressible abdominal bleeding accounts for significant mortality in both military and civilian populations. There is an emergent need for a temporary hemostatic intervention whenever surgical care is not immediately available. Our team previously described a self-expanding polyurethane foam for the treatment of exsanguinating abdominal hemorrhage. The objective of this study was to translate a safe and effective swine dose into an appropriate human dose through foam administration in recently deceased humans with representative tissue compliance. METHODS: With institutional review board oversight and informed consent at three centers, terminal patients were identified. Within 3 hours of death, the abdomen was accessed, and fluid was added to simulate hemorrhage. Foam was percutaneously administered using a prototype delivery system at multiple doses (45, 55, 65, 75, and 100 mL). Intra-abdominal

pressure was monitored for 15 minutes, and then, foam was removed via laparotomy to assess abdominal tissue contact. RESULTS: Twenty-one recently deceased patients ranging in age from 20 years to 92 years and body mass index from 18 kg/m to 39 kg/m were enrolled in the study. Foam was administered at a mean (SD) of 146 (34) minutes after death. Three subjects were screen failures, and three subjects were excluded from the analysis because of experimental errors. Change in intra-abdominal pressure and semiquantitative organ contact were used as surrogates to compare findings between humans and swine. Doses of 45, 55, and 65 mL resulted in peak pressures of 37 (20), 28 (8.1), and 33 (20) mmHg, respectively, within the acceptable range established in swine studies. Foam deployments of 75 mL and 100 mL exceeded acceptable pressures defined in swine. Higher foam doses tended to improve contact with the diaphragm, paracolic gutters, and liver. CONCLUSION: The use of recently deceased humans demonstrates a novel approach to device evaluation in representative human anatomy, particularly when tissue compliance is critical. Sixty-five milliliters was determined to be the clinically appropriate dose for foam treatment in bleeding human patients.

Mhawech-Fauceglia, P., Yan, L., Sharifian, M., Ren, X., Liu, S., Kim, G., et al. (2015). Stromal expression of fibroblast activation protein alpha (FAP) predicts platinum resistance and shorter recurrence in patients with epithelial ovarian cancer. *Cancer Microenvironment, 8*(1), 23-31. The microenvironment plays an important role in tumorigenesis. Fibroblast activation protein alpha (FAP) is overexpressed by fibroblasts present in the microenvironment of many tumors. High FAP expression is a negative prognostic factor in several malignancies, but this has not been investigated in epithelial ovarian cancer (EOC). The aim of this study is to define the value of FAP in EOC. Immunohistochemical staining using an anti-FAP antibody was performed on 338 EOC tissues. mRNA levels in cancer cell lines and FAP silencing using siRNA was also done. FAP immunoexpression by tumor stroma was a significant predictive factor for platinum resistance ($p = 0.0154$). In survival analysis of days to recurrence, FAP stoma+ was associated with shorter recurrence than those with FAP− stroma ($p = 0.0247$). In 21.8 % of tumors, FAP protein was expressed by the tumor epithelium, and FAP mRNA was more highly expressed in tumors ($n = 489$) than in normal tissues ($n = 8$) ($p = 3.88 \times 10-4$). In vitro, addition of FAP to EOC cells induced a 10–12 % increase in cell viability both in the presence and absence of cisplatin.

Conversely, siRNA silencing of FAP resulted in ~10 % reduction in EOC cell proliferation. We have shown that FAP expression in EOC is associated with poorer clinical outcomes. FAP may have novel cell-autonomous effects suggesting that targeting FAP could have pleiotropic anti-tumor effects, and anti-FAP therapy could be a highly effective novel treatment for EOC, especially in cisplatinum-resistant cases.

Mooney, M. A., & Wilmot, B. (2015). Gene set analysis: A step-by-step guide. *American Journal of Medical Genetics.Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*,

To maximize the potential of genome-wide association studies, many researchers are performing secondary analyses to identify sets of genes jointly associated with the trait of interest. Although methods for gene-set analyses (GSA), also called pathway analyses, have been around for more than a decade, the field is still evolving. There are numerous algorithms available for testing the cumulative effect of multiple SNPs, yet no real consensus in the field about the best way to perform a GSA. This paper provides an overview of the factors that can affect the results of a GSA, the lessons learned from past studies, and suggestions for how to make analysis choices that are most appropriate for different types of data.

Moren, A., Cook, M., McClain, M., Doberne, J., Kiraly, L., Perkins, R. S., et al. (2015). A pilot curriculum in international surgery for medical students. *Journal of Surgical Education, 72*(4), e9-e14.

BACKGROUND: As medical student interest in global surgical care grows, a comprehensive curriculum is necessary to understand surgical care in resource-limited environments. METHODS: We developed a surgical elective encompassing a multiyear medical student curriculum, with the goal of improving students' understanding of global surgical care, consisting of a junior seminar and a senior clerkship. This student elective focused on the global burden of surgical disease, ethics of care in low-resource settings, and care of marginalized U.S. POPULATIONS: Students who participated in the fourth year clerkship at a tertiary center in Northern India completed a reflective essay on their experience. Qualitative analysis was conducted using constant comparison and axial coding to establish a grounded theory. RESULTS: Medical students showed

a desire to serve the poor, build collaborative relationships, and integrate international health into their future career. CONCLUSIONS: This novel curriculum provides students a clinical and public health basis to understand challenges of surgical care in low-resource environments while laying the groundwork for students with a future career in global health.

Morgan, T. K., & Berlin, M. (2015). Immunocytochemical analysis of the cervical pap smear. *Methods in Molecular Biology (Clifton, N.J.), 1249*, 203-212.

Although immunostained cervical Pap smears are not yet FDA approved for clinical use, it is very likely that they will become widely employed in the near future to identify neoplastic squamous and iendocervical glandular cells when screening liquid-based cytological preparations (i.e., SurePath or ThinPrep). The current problem with cytology complemented by high-risk human papillomavirus (HPV) testing is poor specificity. HPV testing provides superior sensitivity, but many women are infected with the virus, while very few have had persistent infections leading to carcinoma. Pathologists routinely use antibodies directed against the cyclin-dependent kinase inhibitor p16 (p16(INK4a)) or a combination of antibodies directed against topoisomerase-2-alpha and minichromosome maintenance protein-2 (as in ProEx C) to improve diagnostic precision and accuracy in cervical tissue biopsies. This chapter will describe the immunocytochemical methods used by our group to immunostain cervical Pap smears and provide significantly improved positive predictive value when screening for cervical cancer.

Muench, J., Jarvis, K., Gray, M., Hayes, M., Vandersloot, D., Hardman, J., et al. (2015). Implementing a team-based SBIRT model in primary care clinics. *Journal of Substance use, 20*(2), 106-112.

Background and aim: Six Oregon primary care clinics integrated a team-based, systematized alcohol and drug Screening, Brief Intervention, Referral to Treatment (SBIRT) process into their standard clinic workflow. Clinic staff administered screening forms and brief assessments, and clinicians were trained to perform brief interventions and treatment referrals when needed. Methods: Patient-level data from the electronic health record (EHR) were used to calculate implementation rates in each clinic-specifically, how often each step of a 3-step SBIRT process was performed when indicated. Rates were tracked on a quarterly basis over 2 years. Results: Implementation rates increased over time for screening and assessment tasks performed by

clinic staff, but not for brief interventions performed by clinicians. Averaged over time, annual screens were given to approximately 44% of eligible patients, brief assessments to around 66% of eligible patients, and brief interventions to about 40% of those eligible. Considerable variability existed across individual clinics, some of which demonstrated notably high rates. Conclusion: A team-based approach to SBIRT in primary care settings capitalizes on the medical home model but also creates unique challenges. Facilitative EHR tools are necessary.

Muench, J., Jarvis, K., Vandersloot, D., Hayes, M., Nash, W., Hardman, J., et al. (2015). Perceptions of clinical team members toward implementation of SBIRT processes. *Alcoholism Treatment Quarterly*, *33*(2), 143-160.

This study implemented a systematized, team-based Screening, Brief Intervention, Referral to Treatment (SBIRT) process in six primary care clinics that incorporated efforts of receptionists, medical assistants, and physicians. Focus groups were conducted to identify key facilitators of and barriers to successful implementation. Buy-in from physicians and clinic leadership and seamless integration of SBIRT into the electronic medical record were noted as the strongest facilitators. Time constraints and personal discomfort discussing substance use were cited as major barriers. A team-based approach to SBIRT in primary care settings capitalizes on the medical home model but also creates unique barriers.

Nabavizadeh, N., Shukla, R., Elliott, D. A., Mitin, T., Vaccaro, G. M., Dolan, J. P., et al. (2015). Preoperative carboplatin and paclitaxel-based chemoradiotherapy for esophageal carcinoma: Results of a modified CROSS regimen utilizing radiation doses greater than 41.4 gy. *Diseases of the Esophagus : Official Journal of the International Society for Diseases of the Esophagus / I.S.D.E*,

Trimodality therapy for resectable esophageal and gastroesophageal junction cancers utilizing preoperative radiotherapy with concurrent carboplatin and paclitaxel-based chemotherapy is being increasingly utilized secondary to the results of the phase III CROSS trial. However, there is a paucity of reports of this regimen as a component of chemoradiotherapy in North America. We aim to report on our clinical experience using a modified CROSS regimen with higher

radiotherapy doses. Patients with advanced (cT2-cT4 or node positive) esophageal or gastroesophageal junction carcinoma who received preoperative carboplatin/paclitaxel-based chemoradiotherapy with radiation doses of greater than 41.4 Gray (Gy) followed by esophagectomy were identified from an institutional database. Patient, imaging, treatment, and tumor response characteristics were analyzed. Twenty-four patients were analyzed. All but one tumor had adenocarcinoma histology. The median radiation dose was 50.4 Gy. Pathologic complete response was achieved in 29% of patients, with all receiving 50.4 Gy. Three early postoperative deaths were seen, due in part to acute respiratory distress syndrome and all three patients received 50-50.4 Gy. With a median follow-up of 9.4 months (23 days-2 years), median survival was 24 months. Trimodality therapy utilizing concurrent carboplatin/paclitaxel with North American radiotherapy doses appeared to have similar pathologic complete response rates compared with the CROSS trial, but may be associated with higher toxicity. Although the sample size is small and further follow-up is necessary, radiation doses greater than 41.4 Gy may not be warranted secondary to a potentially increased risk of severe radiation-induced acute lung injury.

Nakano, M. M., Kominos-Marvell, W., Sane, B., Nader, Y. M., Barendt, S. M., Jones, M. B., et al. (2014). spxA2, encoding a regulator of stress resistance in bacillus anthracis, is controlled by SaiR, a new member of the Rrf2 protein family. *Molecular Microbiology, 94*(4), 815-827.
Spx, a member of the ArsC (arsenate reductase) protein family, is conserved in Gram-positive bacteria, and interacts with RNA polymerase to activate transcription in response to toxic oxidants. In Bacillus anthracis str. Sterne, resistance to oxidative stress requires the activity of two paralogues, SpxA1 and SpxA2. Suppressor mutations were identified in spxA1 mutant cells that conferred resistance to hydrogen peroxide. The mutations generated null alleles of the saiR gene and resulted in elevated spxA2 transcription. The saiR gene resides in the spxA2 operon and encodes a member of the Rrf2 family of transcriptional repressors. Derepression of spxA2 in a saiR mutant required SpxA2, indicating an autoregulatory mechanism of spxA2 control. Reconstruction of SaiR-dependent control of spxA2 was accomplished in Bacillus subtilis, where deletion analysis uncovered two cis-elements within the spxA2 regulatory region that are required for repression. Mutations to one of the sequences of dyad symmetry substantially reduced SaiR binding and SaiR-dependent repression of transcription from the spxA2 promoter in

vitro. Previous studies have shown that spxA2 is one of the most highly induced genes in a macrophage infected with B. anthracis. The work reported herein uncovered a key regulator, SaiR, of the Spx system of stress response control.

Nan, X., Tamguney, T. M., Collisson, E. A., Lin, L. J., Pitt, C., Galeas, J., et al. (2015). Ras-GTP dimers activate the mitogen-activated protein kinase (MAPK) pathway. *Proceedings of the National Academy of Sciences of the United States of America*,

Rat sarcoma (Ras) GTPases regulate cell proliferation and survival through effector pathways including Raf-MAPK, and are the most frequently mutated genes in human cancer. Although it is well established that Ras activity requires binding to both GTP and the membrane, details of how Ras operates on the cell membrane to activate its effectors remain elusive. Efforts to target mutant Ras in human cancers to therapeutic benefit have also been largely unsuccessful. Here we show that Ras-GTP forms dimers to activate MAPK. We used quantitative photoactivated localization microscopy (PALM) to analyze the nanoscale spatial organization of PAmCherry1-tagged KRas 4B (hereafter referred to KRas) on the cell membrane under various signaling conditions. We found that at endogenous expression levels KRas forms dimers, and KRasG12D, a mutant that constitutively binds GTP, activates MAPK. Overexpression of KRas leads to formation of higher order Ras nanoclusters. Conversely, at lower expression levels, KRasG12D is monomeric and activates MAPK only when artificially dimerized. Moreover, dimerization and signaling of KRas are both dependent on an intact CAAX (C, cysteine; A, aliphatic; X, any amino acid) motif that is also known to mediate membrane localization. These results reveal a new, dimerization-dependent signaling mechanism of Ras, and suggest Ras dimers as a potential therapeutic target in mutant Ras-driven tumors.

Narayana, J., & Horton, W. A. (2015). FGFR3 biology and skeletal disease. *Connective Tissue Research*, , 1-18.

Fibroblast Growth Factor Receptor 3 (FGFR3) is one of four high-affinity receptors for canonical FGF ligands. It acts in many tissues and plays a special role in skeletal development, especially post-embryonic bone growth, where it inhibits chondrocyte proliferation and differentiation. Gain of function mutations cause the most common forms of dwarfism in humans, and they are also

detected in cancer. Triggered by ligand binding or in some cases mutation, FGFR3 activation involves dimerization of receptor monomers, phosphorylation of specific tyrosine residues in the receptor's kinase domain and in the tightly linked scaffold protein Fibroblast Receptor Factor Substrate 2 (FRS2). Signaling molecules recruited to these phosphorylation sites propagate signals through cascades that are subject to modulation. Signal output is also regulated by the fate of the receptor and the interval between its activation and degradation. Trafficking pathways have been identified for both lysosomal and proteasomal degradation, as well as, an alternative fate that involves intramembrane cleavage that produces an intracellular domain fragment capable of nuclear transport and potential function.

Nasrallah, H. A., Harvey, P. D., Casey, D., Csoboth, C. T., Hudson, J. I., Julian, L., et al. (2015). The management of schizophrenia in clinical practice (MOSAIC) registry: A focus on patients, caregivers, illness severity, functional status, disease burden and healthcare utilization. *Schizophrenia Research*,

BACKGROUND: The Management of Schizophrenia in Clinical Practice (MOSAIC), a disease-based registry of schizophrenia, was initiated in December 2012 to address important gaps in our understanding of the impact and burden of schizophrenia and to provide insight into the current status of schizophrenia care in the US. Recruitment began in December 2012 with ongoing assessment continuing through May 2014. METHODS: Participants were recruited from a network of 15 centralized Patient Assessment Centers supporting proximal care sites. Broad entry criteria included patients diagnosed with schizophrenia, schizophreniform or schizoaffective disorder, presenting within the normal course of care, in usual treatment settings, aged >/=18years and able to read and speak English. RESULTS: By May 2014, 550 participants (65.8% male, 59.8% White, 64.4% single, mean age 42.9years), were enrolled. The majority had a diagnosis of schizophrenia (62.0%). Mean illness duration at entry was 15.0years. Common comorbidities at entry were high lipid levels (26.9%), hypertension (23.1%) and type II diabetes (13%). Participants were categorized by baseline overall Clinical Global Impression-Schizophrenia Severity Score as minimally (9.1%), mildly (25.3%), moderately (39.9%), markedly (22.3%) and severely (3.4%) ill. Most commonly used second generation antipsychotics at entry were risperidone (17.8%), clozapine (16.5%), olanzapine (14.0%), aripiprazole (13.6%) and

quetiapine (5.6%). CONCLUSIONS: No large-scale patient registry has been conducted in the US to longitudinally follow patients with schizophrenia and describe symptom attributes, support network, care access and disease burden. These data provide important epidemiological, clinical and outcome insights into the burden of schizophrenia in the US.

Naugler, W. E., Tarlow, B. D., Fedorov, L. M., Taylor, M., Pelz, C., Li, B., et al. (2015). Fibroblast growth factor signaling controls liver size in mice with humanized livers. *Gastroenterology*, BACKGROUND & AIMS: The ratio of liver size to body weight (hepatostat) is tightly controlled, but little is known about how the physiologic functions of the liver help determine its size. Livers of mice repopulated with human hepatocytes (humanized livers) grow to larger than normal; the human hepatocytes do not recognize fibroblast growth factor-15 (FGF15) produced by mouse intestine. This results in upregulation of bile acid synthesis in the human hepatocytes and enlargement of the bile acid pool. We investigated whether abnormal bile acid signaling affects the hepatostat in mice. METHODS: We crossed Fah-/-, Rag2-/-, Il2r-/- mice with NOD mice to create FRGN mice, whose livers can be fully repopulated with human hepatocytes. We inserted the gene for human FGF19 (ortholog to mouse Fgf15), including regulatory sequences, into the FRGN mice to create FRGN19+ mice. Livers of FRGN19+ mice and their FRGN littermates were fully repopulated with human hepatocytes. Liver tissues were collected and bile acid pool sizes and RNA sequences were analyzed and compared with those of mice without humanized livers (controls). RESULTS: Livers were larger in FRGN mice with humanized livers (13% of body weight), compared to control FRGN mice; they also had much larger bile acid pools and aberrant bile acid signaling. Livers from FRGN19+ normalized to 7.8% of body weight, and their bile acid pool and signaling more closely resembled that of control FRGN19+ mice. RNA sequence analysis showed activation of the Hippo pathway, and immunohistochemical and transcription analyses revealed increased hepatocyte proliferation, but not apoptosis, in the enlarged humanized livers of FRGN mice. Cell sorting experiments showed that although healthy human liver does not produce FGF19, non-parenchymal cells from cholestatic livers produce FGF19. CONCLUSIONS: In mice with humanized livers, expression of an FGF19 transgene corrects bile acid signaling defects, resulting in normalization of bile acid synthesis, the bile acid pool, and liver size. These

findings indicate that liver size is, in part, regulated by the size of the bile acid pool that the liver must circulate.

Nguyen, D. L., Palmer, L. B., Nguyen, E. T., McClave, S. A., Martindale, R. G., & Bechtold, M. L. (2015). Specialized enteral nutrition therapy in crohn's disease patients on maintenance infliximab therapy: A meta-analysis. *Therapeutic Advances in Gastroenterology, 8*(4), 168-175.

Objectives: Many patients with Crohns disease on infliximab maintenance therapy have recurrent symptoms despite an initial clinical response. Therefore, concomitant therapies have been studied. We conducted a meta-analysis to assess the effect of specialized enteral nutrition therapy with infliximab versus infliximab monotherapy in patients with Crohns disease. Methods: A comprehensive search of multiple databases was performed. All studies of adult patients with Crohns disease comparing specialized enteral nutrition therapy (elemental or polymeric diet with low-fat or regular diet) with infliximab versus infliximab monotherapy without dietary restrictions were included. Meta-analysis was performed using the Mantel Haenszel (fixed effect) model with odds ratio (OR) to assess for clinical remission. Results: Four studies (n = 342) met inclusion criteria. Specialized enteral nutrition therapy with infliximab resulted in 109 of 157 (69.4%) patients reaching clinical remission compared with 84 of 185 (45.4%) with infliximab monotherapy [OR 2.73; 95% confidence interval (CI): 1.734.31, p ≤ 0.01]. Similarly, 79 of 106 (74.5%) patients receiving enteral nutrition therapy and infliximab remained in clinical remission after one year compared with 62 of 126 (49.2%) patients receiving infliximab monotherapy (OR 2.93; 95% CI: 1.665.17, p ≤ 0.01). No publication bias or heterogeneity was noted for either outcome. Conclusions: The use of specialized enteral nutrition therapy in combination with infliximab appears to be more effective at inducing and maintaining clinical remission among patients with Crohns disease than infliximab monotherapy. © The Author(s), 2015.

Norris, S. L., Holmer, H. K., Fu, R., Ogden, L. A., Viswanathan, M. S., & Abou-Setta, A. M. (2014). Clinical trial registries are of minimal use for identifying selective outcome and analysis reporting. *Research Synthesis Methods, 5*(3), 273-284.

OBJECTIVE: This study aimed to examine selective outcome reporting (SOR) and selective analysis reporting (SAR) in randomized controlled trials (RCTs) and to explore the usefulness of

trial registries for identifying SOR and SAR. STUDY DESIGN AND SETTING: We selected one "index outcome" for each of three comparative effectiveness reviews (CERs) of pharmacotherapy and extracted data on this outcome from trial registries and from study publications. RESULTS: Among 50 RCTs published since 2005 and reporting the index outcome, only 50% were listed in registries; 90% of RCTs were assessed as having SOR or SAR. The index outcome in the registry was different from that in the publication in 75% of trials in two CERs, and not specified at all in the third. Reported outcomes and analyses were not consistent between the publication's methods section and the results section in 33% and 46% of the two CERs where the index outcome was a benefit. There were no statistically significant predictors of SOR and SAR in our small sample where some predictors lacked variability. CONCLUSION: The SOR and SAR were frequent in this pilot study, and the most common type of SOR was the publication of outcomes that were not pre-specified. Trial registries were of little use in identifying SOR and of no use in identifying SAR.

Novak, D. J., Bai, Y., Cooke, R. K., Marques, M. B., Fontaine, M. J., Gottschall, J. L., et al. (2015). Making thawed universal donor plasma available rapidly for massively bleeding trauma patients: Experience from the pragmatic, randomized optimal platelets and plasma ratios (PROPPR) trial. *Transfusion, 55*(6), 1331-1339.

BACKGROUND: The Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial was a randomized clinical trial comparing survival after transfusion of two different blood component ratios for emergency resuscitation of traumatic massive hemorrhage. Transfusion services supporting the study were expected to provide thawed plasma, platelets, and red blood cells within 10 minutes of request. STUDY DESIGN AND METHODS: At the 12 Level 1 trauma centers participating in PROPPR, blood components transfused and delivery times were tabulated, with a focus on universal donor (UD) plasma management. The adequacy of site plans was assessed by comparing the bedside blood availability times to study goals and the new American College of Surgeons guidelines. RESULTS: Eleven of 12 sites were able to consistently deliver 6 units of thawed UD plasma to their trauma-receiving unit within 10 minutes and 12 units in 20 minutes. Three sites used blood group A plasma instead of AB for massive transfusion without complications. Approximately 4700 units of plasma were given to the 680 patients enrolled in the

trial. No site experienced shortages of AB plasma that limited enrollment. Two of 12 sites reported wastage of thawed AB plasma approaching 25% of AB plasma prepared. CONCLUSION: Delivering UD plasma to massively hemorrhaging patients was accomplished consistently and rapidly and without excessive wastage in high-volume trauma centers. The American College of Surgeons Trauma Quality Improvement Program guidelines for massive transfusion protocol UD plasma availability are practicable in large academic trauma centers. Use of group A plasma in trauma resuscitation needs further study. © 2015 AABB.

Novosad, D., Follansbee, J., Banfe, S., & Bloom, J. D. (2014). Statewide survey of living arrangements for conditionally released insanity acquittees. *Behavioral Sciences & the Law, 32*(5), 659-665.

There is a large population (n =389) of insanity acquittees on monitored conditional release in Oregon. This article focuses on the living situation for these individuals, which can range from a secure residential treatment facility to independent living. This article will define all the different placement options available and then review the current living situation for all conditionally released insanity acquittees in the state of Oregon on a single day, February 1, 2014. This article shows that the majority of individuals on conditional release live in the most highly structured settings available. The article then ends with a discussion of these findings, including a comparison of current placement options, with previous descriptions in the literature demonstrating that current community options offer more structure and more individuals reside in structured settings than was previously the case. Current findings will be related to inpatient psychiatric bed reduction strategies and the question of possible transinstitutionalization.

Noyd, D. H., & Sharp, T. M. (2015). Recent advances in dengue: Relevance to puerto rico. *Puerto Rico Health Sciences Journal, 34*(2), 65-70.

Dengue represents an increasingly important public health challenge in Puerto Rico, with recent epidemics in 2007, 2010, and 2012-2013. Although recent advances in dengue vaccine development offer hope for primary prevention, the role of health professionals in the diagnosis and management of dengue patients is paramount. Case definitions for dengue, dengue with warning signs, and severe dengue provide a framework to guide clinical decision-making. Furthermore, the differentiation between dengue and other acute febrile illnesses, such as

leptospirosis and chikungunya, is necessary for the appropriate diagnosis and management of cases. An understanding of dengue epidemiology and surveillance in Puerto Rico provides context for clinicians in epidemic and non-epidemic periods. This review aims to improve health professionals' ability to diagnose dengue, and as highlight the relevance of recent advances in dengue prevention and management in Puerto Rico.

Ochs, C., Perl, Y., Geller, J., Haendel, M., Brush, M., Arabandi, S., et al. (2015). Summarizing and visualizing structural changes during the evolution of biomedical ontologies using a diff abstraction network. *Journal of Biomedical Informatics*,
Biomedical ontologies are a critical component in biomedical research and practice. As an ontology evolves, its structure and content change in response to additions, deletions and updates. When editing a biomedical ontology, small local updates may affect large portions of the ontology, leading to unintended and potentially erroneous changes. Such unwanted side effects often go unnoticed since biomedical ontologies are large and complex knowledge structures. Abstraction networks, which provide compact summaries of an ontology's content and structure, have been used to uncover structural irregularities, inconsistencies and errors in ontologies. In this paper, we introduce Diff Abstraction Networks ("Diff AbNs"), compact networks that summarize and visualize global structural changes due to ontology editing operations that result in a new ontology release. A Diff AbN can be used to support curators in identifying unintended and unwanted ontology changes. The derivation of two Diff AbNs, the Diff Area Taxonomy and the Diff Partial-area Taxonomy, is explained and Diff Partial-area Taxonomies are derived and analyzed for the Ontology of Clinical Research, Sleep Domain Ontology, and Eagle-I Research Resource Ontology. Diff Taxonomy usage for identifying unintended erroneous consequences of quality assurance and ontology merging are demonstrated.

O'Neal, S. E., & Flecker, R. H. (2015). Hospitalization frequency and charges for neurocysticercosis, united states, 2003–2012. *Emerging Infectious Diseases*, *21*(6), 969-976.
Neurocysticercosis, brain infection with Taenia solium larval cysts, causes substantial neurologic illness around the world. To assess the effect of neurocysticercosis in the United States, we reviewed hospitalization discharge data in the Nationwide Inpatient Sample for 2003–2012 and

found an estimated 18,584 hospitalizations for neurocysticercosis and associated hospital charges totaling >US $908 million. The risk for hospitalization was highest among Hispanics (2.5/100,000 population), a rate 35 times higher than that for the non-Hispanic white population. Nearly three-quarters of all hospitalized patients with neurocysticercosis were Hispanic. Male sex and age 20–44 years also incurred increased risk. In addition, hospitalizations and associated charges related to cysticercosis far exceeded those for malaria and were greater than for those for all other neglected tropical diseases combined. Neurocysticercosis is an increasing public health concern in the United States, especially among Hispanics, and costs the US health care system a substantial amount of money.

Ostrowski, K. A., & Walsh, T. J. (2015). Infertility with testicular cancer. *Urologic Clinics of North America*,

Testicular germ cell cancer is one of the most curable cancers. Most patients are treated during their reproductive years, making infertility a significant quality of life issue after successful treatment. This focused review evaluates the factors that contribute to infertility and specific fertility risks with the various testicular cancer treatments. Timing of patient discussions and current fertility treatments are reviewed.

Palejwala, N. V., Gale, M. J., Clark, R. F., Schlechter, C., Weleber, R. G., & Pennesi, M. E. (2015). Insights into autosomal dominant stargardt-like macular dystrophy through multimodality diagnostic imaging. *Retina (Philadelphia, Pa.)*,

PURPOSE: Autosomal dominant Stargardt-like macular dystrophy is a rare juvenile macular dystrophy most commonly because of mutations in ELOVL4 and PROM1 genes. In this study, we review a series of cases of Stargardt-like macular dystrophy and use advanced imaging techniques to describe pathophysiologic manifestations. METHODS: A retrospective medical record review was performed for five patients from two families with ELOVL4 mutation and one patient with PROM1 mutation including reviewing diagnostic imaging, such as fundus photography, spectral domain optical coherence tomography, fundus autofluorescence, and adaptive optics flood-illuminated photography. RESULTS: All patients had reduced central visual acuity with varying degree of foveal atrophy. In the ELOVL4 group, best-corrected visual acuity

ranged from 20/25 to 20/200. Early pathologic changes included thickening of the external limiting membrane and outer nuclear atrophy followed by retinal pigment epithelium loss in later stages. Adaptive optics imaging revealed photoreceptor loss even in early stages with good visual acuity. The PROM1 patient also had similar central vision loss with significant outer nuclear atrophy. In contrast to ELOVL4 mutation, there was more diffuse and patchy retinal pigment epithelium loss throughout the macula. CONCLUSION: Both ELOVL4- and PROM1-related maculopathies are characterized by progressive photoreceptor atrophy and central vision loss. Using advanced diagnostic imaging, early disease changes and disease progression can be characterized.

Papay, F., Taub, P. J., Doumit, G., Flores, R. L., Kuang, A. A., Mlynek, K., et al. (2015). The american society of maxillofacial surgery preceptorship program: A product of the 2013 american society of maxillofacial surgery executive board strategy session and survey. *The Journal of Craniofacial Surgery*, *26*(4), 1156-1158.

One of the main goals of the American Society of Maxillofacial Surgery (ASMS) is to develop educational programs that increase expertise in maxillofacial surgery. We describe the outline of the new ASMS Preceptorship Program, a collective effort by ASMS members to increase access to all areas of maxillofacial surgery. Furthermore, we discuss the original survey pertinent to the development of this program, the results of the survey, and specifics regarding the structure of the program. We hope for the preceptorship program to be an excellent resource for members to mentor one another, develop intellectual and academic curiosity, provide avenues for collaboration, and further the ASMS's role in shaping maxillofacial surgery into the future.

Papesh, M. A., Billings, C. J., & Baltzell, L. S. (2015). Background noise can enhance cortical auditory evoked potentials under certain conditions. *Clinical Neurophysiology*, *126*(7), 1319-1330.

Objective: To use cortical auditory evoked potentials (CAEPs) to understand neural encoding in background noise and the conditions under which noise enhances CAEP responses. Methods: CAEPs from 16 normal-hearing listeners were recorded using the speech syllable/ba/presented in quiet and speech-shaped noise at signal-to-noise ratios of 10 and 30 dB. The syllable was presented binaurally and monaurally at two presentation rates. Results: The amplitudes of N1

and N2 peaks were often significantly enhanced in the presence of low-level background noise relative to quiet conditions, while P1 and P2 amplitudes were consistently reduced in noise. P1 and P2 amplitudes were significantly larger during binaural compared to monaural presentations, while N1 and N2 peaks were similar between binaural and monaural conditions. Conclusions: Methodological choices impact CAEP peaks in very different ways. Negative peaks can be enhanced by background noise in certain conditions, while positive peaks are generally enhanced by binaural presentations. Significance: Methodological choices significantly impact CAEPs acquired in quiet and in noise. If CAEPs are to be used as a tool to explore signal encoding in noise, scientists must be cognizant of how differences in acquisition and processing protocols selectively shape CAEP responses. © 2014 .

Parameswaran, S., Dravid, S. M., Teotia, P., Krishnamoorthy, R. R., Qiu, F., Toris, C., et al. (2015). Continuous non-cell autonomous reprogramming to generate retinal ganglion cells for glaucomatous neuropathy. *Stem Cells, 33*(6), 1743-1758.

Glaucoma, where the retinal ganglion cells (RGCs) carrying the visual signals from the retina to the visual centers in the brain are progressively lost, is the most common cause of irreversible blindness. The management approaches, whether surgical, pharmacological, or neuroprotective do not reverse the degenerative changes. The stem cell approach to replace dead RGCs is a viable option but currently faces several barriers, such as the lack of a renewable, safe, and ethical source of RGCs that are functional and could establish contacts with bona fide targets. To address these barriers, we have derived RGCs from the easily accessible adult limbal cells, reprogrammed to pluripotency by a non-nucleic acid approach, thus circumventing the risk of insertional mutagenesis. The generation of RGCs from the induced pluripotent stem (iPS) cells, also accomplished non-cell autonomously, recapitulated the developmental mechanism, ensuring the predictability and stability of the acquired phenotype, comparable to that of native RGCs at biochemical, molecular, and functional levels. More importantly, the induced RGCs expressed axonal guidance molecules and demonstrated the potential to establish contacts with specific targets. Furthermore, when transplanted in the rat model of ocular hypertension, these cells incorporated into the host RGC layer and expressed RGC-specific markers. Transplantation of these cells in immune-deficient mice did not produce tumors. Together, our results posit retinal

progenitors generated from non-nucleic acid-derived iPS cells as a safe and robust source of RGCs for replacing dead RGCs in glaucoma. © 2015 AlphaMed Press.

Parunov, L. A., Surov, S. S., Tucker, E., & Ovanesov, M. V. (2015). No effect of corn trypsin inhibitor on factor XIa-dependent thrombin generation assay: Comment. *Journal of Thrombosis and Haemostasis : JTH,*

Corn trypsin inhibitor (CTI) is a well-characterized inhibitor of coagulation Factor (F) XIIa that is commonly used as a reagent in the tissue factor (TF)-activated global hemostasis assays, Thrombin Generation Test (TGT) and Thromboelastography (1-3). CTI was shown to improve assay reproducibility (4) presumably because CTI inhibits spontaneous plasma activation caused by contact with collection tubes, pipette tips, storage vials and experimental cuvettes. The effect of CTI against contact artifacts is concentration-dependent from 5 up to a saturation concentration of 100 mug/mL, and therefore 100 mug/mL or more CTI is widely used in experiments (5). Although spontaneous contact activation can also be mitigated by higher concentrations of TF (>5 pM), low TF (</=1 pM) and hence CTI are required in certain situations (4), e.g., for evaluation of FIX, FVIII and FXI deficiencies.

Pazos, M., Yang, H., Gardiner, S. K., Cepurna, W. O., Johnson, E. C., Morrison, J. C., et al. (2015). Rat optic nerve head anatomy within 3D histomorphometric reconstructions of normal control eyes. *Experimental Eye Research,*

The purpose of this study is to three-dimensionally (3D) characterize the principal macroscopic and microscopic relationships within the rat optic nerve head (ONH) and quantify them in normal control eyes. Perfusion-fixed, trephinated ONH from 8 normal control eyes of 8 Brown Norway Rats were 3D histomorphometrically reconstructed, visualized, delineated and parameterized. The rat ONH consists of 2 scleral openings, (a superior neurovascular and inferior arterial) separated by a thin connective tissue strip we have termed the "scleral sling". Within the superior opening, the nerve abuts a prominent extension of Bruch's Membrane (BM) superiorly and is surrounded by a vascular plexus, as it passes through the sclera, that is a continuous from the choroid into and through the dural sheath and contains the central retinal vein (CRV), (inferiorly).

The inferior scleral opening contains the central retinal artery and three long posterior ciliary arteries which obliquely pass through the sclera to obtain the choroid. Bruch's Membrane Opening (BMO) is irregular and vertically elongated, enclosing the nerve (superiorly) and CRV and CRA (inferiorly). Overall mean BMO Depth, BMO Area, Choroidal Thickness and peripapillary Scleral Thickness were 29 mum, 56.5 x 103 mum2, 57 mum and 105 mum respectively. Mean anterior scleral canal opening (ASCO) and posterior scleral canal opening (PSCO) radii were 201 +/- 14 mum and 204 +/- 17 mum, respectively. Mean optic nerve area at the ASCO and PSCO were 46.3 x 103+/-9.5 x 103 mum2 and 44.2 x 103+/-9.7 x 103 mum2 respectively. In conclusion, the 3D complexity of the rat ONH and the extent to which it differs from the primate have been under-appreciated within previous 2D studies. Properly understood, these anatomic differences may provide new insights into the relative susceptibilities of the rat and primate ONH to elevated intraocular pressure.

Pechauer, A. D., Jia, Y., Liu, L., Gao, S. S., Jiang, C., & Huang, D. (2015). Optical coherence tomography angiography ofPeripapillary retinal blood flow response to hyperoxia. *Investigative Ophthalmology & Visual Science*, *56*(5), 3287-3291.

PURPOSE: To measure the change in peripapillary retinal blood flow in response to hyperoxia by using optical coherence tomography (OCT) angiography. METHODS: One eye of each healthy human participants (six) was scanned with a commercial high-speed (70 kHz) spectral OCT. Scans were captured twice after 10-minute exposures to normal breathing (baseline) and hyperoxia. Blood flow was detected by the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. Peripapillary retinal blood flow index and vessel density were calculated from en face maximum projections of the retinal layers. The experiment was performed on 2 separate days for each participant. Coefficient of variation (CV) was used to measure within-day repeatability and between-day reproducibility. Paired t-tests were used to compare means of baseline and hyperoxic peripapillary retinal blood flow. RESULTS: A decrease of 8.87% +/- 3.09% (mean +/- standard deviation) in flow index and 2.61% +/- 1.50% in vessel density was observed under hyperoxia. The within-day repeatability CV of baseline measurements was 5.75% for flow index and 1.67% for vessel density. The between-day reproducibility CV for baseline flow index and vessel density was 11.1% and 1.14%, respectively. The between-day reproducibility of

the hyperoxic response was 3.71% and 1.67% for flow index and vessel density, respectively. CONCLUSIONS: Optical coherence tomography angiography with SSADA was able to detect a decrease in peripapillary retinal blood flow in response to hyperoxia. The response was larger than the variability of baseline measurements. The magnitude of an individual's hyperoxic response was highly variable between days. Thus, reliable assessment may require averaging multiple measurements.

Placzek, A. T., & Scanlan, T. S. (2015). New synthetic routes to thyroid hormone analogs: D6-sobetirome, 3H-sobetirome, and the antagonist NH-3. *Tetrahedron*,

New synthetic routes for the preparation of isotopically labeled versions of thyroid hormone agonist sobetirome were developed using Knochel's iodine-magnesium exchange. A more efficient synthesis of the thyroid hormone antagonist NH-3 was developed from a common intermediate in the sobetirome route. Using the new synthetic routes, d6-and 3H-sobetirome were prepared for their use in studying biodistribution and the cellular uptake of sobetirome. The new route to NH-3 allows for a more rapid and efficient synthesis and provides access to an advanced intermediate to facilitate antagonist analog production in the final bond-forming synthetic step. © 2015.

Promjunyakul, N., Lahna, D., Kaye, J. A., Dodge, H. H., Erten-Lyons, D., Rooney, W. D., et al. (2015). Characterizing the white matter hyperintensity penumbra with cerebral blood flow measures. *NeuroImage.Clinical*, *8*, 224-229.

OBJECTIVE: White matter hyperintensities (WMHs) are common with age, grow over time, and are associated with cognitive and motor impairments. Mechanisms underlying WMH growth are unclear. We aimed to determine the presence and extent of decreased normal appearing white matter (NAWM) cerebral blood flow (CBF) surrounding WMHs to identify 'WM at risk', or the WMH CBF penumbra. We aimed to further validate cross-sectional finding by determining whether the baseline WMH penumbra CBF predicts the development of new WMHs at follow-up. METHODS: Sixty-one cognitively intact elderly subjects received 3 T MPRAGE, FLAIR, and pulsed arterial spin labeling (PASL). Twenty-four subjects returned for follow-up MRI. The inter-scan interval was 18 months. A NAWM layer mask, comprised of fifteen layers, 1 mm thick each surrounding WMHs,

was generated for periventricular (PVWMH) and deep (DWMH) WMHs. Mean CBF for each layer was computed. New WMH and persistent NAWM voxels for each penumbra layer were defined from follow-up MRI. RESULTS: CBF in the area surrounding WMHs was significantly lower than the total brain NAWM, extending approximately 12 mm from both the established PVWMH and DWMH. Voxels with new WMH at follow-up had significantly lower baseline CBF than voxels that maintained NAWM, suggesting that baseline CBF can predict the development of new WMHs over time. CONCLUSIONS: A CBF penumbra exists surrounding WMHs, which is associated with future WMH expansion. ASL MRI can be used to monitor interventions to increase white matter blood flow for the prevention of further WM damage and its cognitive and motor consequences.

Puljic, A., Page, J., & Caughey, A. B. (2015). Reply regarding: The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. *American Journal of Obstetrics and Gynecology*,

Quigg, M., Sun, F., Fountain, N. B., Jobst, B. C., Wong, V. S. S., Mirro, E., et al. (2015). Interrater reliability in interpretation of electrocorticographic seizure detections of the responsive neurostimulator. *Epilepsia*, *56*(6), 968-971.

Objective Electrocorticographic (ECoG) recordings from patients with medically intractable partial-onset seizures treated with a responsive neurostimulator system (the RNS System) that detects and stores physician-specified ECoG events provide a new data resource. Interpretation of these recordings has not yet been validated. The purpose was to evaluate the interrater interpretation of chronic ambulatory ECoG recordings obtained by the RNS System. Methods Five pairs of five experts independently classified 7,221 ECoG recordings obtained from 128 patients with medically intractable partial seizures who participated in a randomized controlled trial of the safety and efficacy of the RNS System. ECoG detections - "long episodes" or "saturations" - were classified as "seizures" or "not seizures" based on a reference definition. Interrater agreement rates and kappa score reliabilities were calculated between rater pairs from the ECoG sample as a whole and within individual patients who had more than the median number of individual ECoG recordings. Results The overall interrater agreement was 79%, with a reliability $\kappa = 0.57$ (moderate agreement). Agreement between pairs of reviewers ranged from 0.69 to 0.85.

Agreement rates were 94% or better for 50% of patients. Only 25% of patients had ECoG recordings agreement rates worse than 75%. ECoGs with mixed interpretations (one reviewer "seizure"/the other - "not seizure") consisted of periods of low amplitude activity that evolved in amplitude or periodic discharges near 2 Hz. Significance Although reliability as a whole was moderate, for the majority of patients, detections yielded highly reliably interpreted events of either electrographic seizures or nonictal epileptiform activity. © 2015 The Authors. Epilepsia published by Wiley Periodicals on behalf of International League Against Epilepsy.

Reddy, R. C., Amodei, R., Estill, C. T., Stormshak, F., Meaker, M., & Roselli, C. E. (2015). Effect of testosterone on neuronal morphology and neuritic growth of fetal lamb hypothalamus-preoptic area and cerebral cortex in primary culture. *PloS One*, *10*(6), e0129521.

Testosterone plays an essential role in sexual differentiation of the male sheep brain. The ovine sexually dimorphic nucleus (oSDN), is 2 to 3 times larger in males than in females, and this sex difference is under the control of testosterone. The effect of testosterone on oSDN volume may result from enhanced expansion of soma areas and/or dendritic fields. To test this hypothesis, cells derived from the hypothalamus-preoptic area (HPOA) and cerebral cortex (CTX) of lamb fetuses were grown in primary culture to examine the direct morphological effects of testosterone on these cellular components. We found that within two days of plating, neurons derived from both the HPOA and CTX extend neuritic processes and express androgen receptors and aromatase immunoreactivity. Both treated and control neurites continue to grow and branch with increasing time in culture. Treatment with testosterone (10 nM) for 3 days significantly ($P < 0.05$) increased both total neurite outgrowth (35%) and soma size (8%) in the HPOA and outgrowth (21%) and number of branch points (33%) in the CTX. These findings indicate that testosterone-induced somal enlargement and neurite outgrowth in fetal lamb neurons may contribute to the development of a fully masculine sheep brain.

Reiss, L. A., Stark, G., Nguyen-Huynh, A. T., Spear, K. A., Zhang, H., Tanaka, C., et al. (2015). Morphological correlates of hearing loss after cochlear implantation and electro-acoustic stimulation in a hearing-impaired guinea pig model. *Hearing Research*,

Hybrid or electro-acoustic stimulation (EAS) cochlear implants (CIs) are designed to provide high-

frequency electric hearing together with residual low-frequency acoustic hearing. However, 30-50% of EAS CI recipients lose residual hearing after implantation. The objective of this study was to determine the mechanisms of EAS-induced hearing loss in an animal model with high-frequency hearing loss. Guinea pigs were exposed to 24 h of noise (12-24 kHz at 116 dB) to induce a high-frequency hearing loss. After recovery, two groups of animals were implanted (n = 6 per group), with one group receiving chronic acoustic and electric stimulation for 10 weeks, and the other group receiving no stimulation during this time frame. A third group (n = 6) was not implanted, but received chronic acoustic stimulation. Auditory brainstem responses were recorded biweekly to monitor changes in hearing. The organ of Corti was immunolabeled with phalloidin, anti-CtBP2, and anti-GluR2 to quantify hair cells, ribbons and post-synaptic receptors. The lateral wall was immunolabeled with phalloidin and lectin to quantify stria vascularis capillary diameters. Bimodal or trimodal diameter distributions were observed; the number and location of peaks were objectively determined using the Aikake Information Criterion and Expectation Maximization algorithm. Noise exposure led to immediate hearing loss at 16-32 kHz for all groups. Cochlear implantation led to additional hearing loss at 4-8 kHz; this hearing loss was negatively and positively correlated with minimum and maximum peaks of the bimodal or trimodal distributions of stria vascularis capillary diameters, respectively. After chronic stimulation, no significant group changes in thresholds were seen; however, elevated thresholds at 1 kHz in implanted, stimulated animals were significantly correlated with decreased presynaptic ribbon and postsynaptic receptor counts. Inner and outer hair cell counts did not differ between groups and were not correlated with threshold shifts at any frequency. As in the previous study in a normal-hearing model, stria vascularis capillary changes were associated with immediate hearing loss after implantation, while little to no hair cell loss was observed even in cochlear regions with threshold shifts as large as 40-50 dB. These findings again support a role of lateral wall blood flow changes, rather than hair cell loss, in hearing loss after surgical trauma, and implicate the endocochlear potential as a factor in implantation-induced hearing loss. Further, the analysis of the hair cell ribbons and post-synaptic receptors suggest that delayed hearing loss may be linked to synapse or peripheral nerve loss due to stimulation excitotoxicity or inflammation. Further research is needed to separate these potential mechanisms of delayed hearing loss.

Riddle, M. C., Yuen, K. C., de Bruin, T. W., Herrmann, K., Xu, J., Ohman, P., et al. (2015). Fixed ratio dosing of pramlintide with regular insulin before a standard meal in patients with type 1 diabetes. *Diabetes, Obesity & Metabolism*,

Amylin is co-secreted with insulin and therefore lacking in type 1 diabetes. Replacement with fixed ratio co-administration of insulin and the amylin analogue pramlintide may be superior to separate dosing. This concept was evaluated in a ratio-finding study. Type 1 diabetes patients were enrolled in a randomized, single-masked, standard-breakfast crossover study using regular human insulin injected simultaneously with pramlintide 6, 9, or 12 mcg/unit insulin, or placebo. Insulin dosage was 30% reduced from participants' usual estimates. Plasma glucose, glucagon, and pramlintide, and adverse events were assessed. All ratios reduced 0-3 hour glucose and glucagon increments >50%. No hypoglycaemia occurred. Adverse events were infrequent and generally mild. All pramlintide/insulin ratios markedly and safely reduced glycaemic excursions and suppressed glucagon secretion in the immediate postprandial state. Further study using one of these ratios to explore the efficacy and safety of longer-term mealtime and basal hormone replacement is warranted.

Rivera, H. M., Christiansen, K. J., & Sullivan, E. L. (2015). The role of maternal obesity in the risk of neuropsychiatric disorders. *Frontiers in Neuroscience, 9*(MAY)

Recent evidence indicates that perinatal exposure to maternal obesity, metabolic disease, including diabetes and hypertension, and unhealthy maternal diet has a long-term impact on offspring behavior and physiology. During the past three decades, the prevalence of both obesity and neuropsychiatric disorders has rapidly increased. Epidemiologic studies provide evidence that maternal obesity and metabolic complications increase the risk of attention deficit hyperactivity disorder, autism spectrum disorders, anxiety, depression, schizophrenia, eating disorders (food addiction, anorexia nervosa, and bulimia nervosa), and cognition in offspring. Animal models of maternal high-fat diet induced obesity also document persistent changes in offspring behavior and impairments in critical neural circuitry. Animals exposed to maternal obesity and high-fat diet consumption display impairments in hyperactivity, social behavior, increased anxiety-like and depressive-like behaviors, substance addiction, food addiction, and diminished cognition. During development, these offspring are exposed to elevated levels of nutrients (fatty acids, glucose),

hormones (leptin, insulin), and inflammatory factors (C-reactive protein, interleukin, and tumor necrosis factor). Such factors appear to permanently change neuroendocrine regulation and brain development in offspring. In addition, inflammation of the offspring brain during gestation impairs the development of neural pathways critical in the regulation of behavior, such as serotoninergic, dopaminergic, and melanocortinergic. Dysregulation of these circuits increases the risk of mental health disorders. Given the high rates of obesity in most developed nations, it is critical that the mechanisms by which maternal obesity programs offspring behavioral are thoroughly characterized. Such knowledge will be critical in the development of preventative strategies and therapeutic interventions.

Rosenbaum, J. T., Choi, D., Wilson, D. J., Grossniklaus, H. E., Harrington, C. A., Dailey, R. A., et al. (2015). Fibrosis, gene expression and orbital inflammatory disease. *The British Journal of Ophthalmology*,

BACKGROUND/AIMS: To clarify the pathogenesis of fibrosis in inflammatory orbital diseases, we analysed the gene expression in orbital biopsies and compared our results with those reported for idiopathic pulmonary fibrosis. METHODS: We collected 140 biopsies from 138 patients (58 lacrimal glands; 82 orbital fat). Diagnoses included healthy controls (n=27), non-specific orbital inflammation (NSOI) (n=61), thyroid eye disease (TED) (n=29), sarcoidosis (n=14) and granulomatosis with polyangiitis (GPA) (n=7). Fibrosis was scored on a 0-3 scale by two experts, ophthalmic pathologists. Gene expression was quantified using Affymetrix U133 plus 2.0 microarray. RESULTS: Within orbital fat, fibrosis was greatest among subjects with GPA (2.75+/-0.46) and significantly increased in tissue from subjects with GPA, NSOI or sarcoidosis ($p<0.01$), but not for TED, compared with healthy controls (1.13+/-0.69). For lacrimal gland, the average score among controls (1.36+/-0.48) did not differ statistically from any of the four disease groups. Seventy-three probe sets identified transcripts correlating with fibrosis in orbital fat (false discovery rate <0.05) after accounting for batch effects, disease type, age and sex. Transcripts with increased expression included fibronectin, lumican, thrombospondin and collagen types I and VIII, each of which has been reported upregulated in pulmonary fibrosis. CONCLUSIONS: A pathologist's recognition of fibrosis in orbital tissue correlates well with increased expression of transcripts that are considered essential in fibrosis. Many transcripts implicated in orbital fibrosis

have been previously implicated in pulmonary fibrosis. TED differs from other causes of orbital fat inflammation because fibrosis is not a major component. Marked fibrosis is less common in the lacrimal gland compared with orbital adipose tissue.

Rozanov, D., Cheltsov, A., Sergienko, E., Vasile, S., Golubkov, V., Aleshin, A. E., et al. (2015). TRAIL-based high throughput screening reveals a link between TRAIL-mediated apoptosis and glutathione reductase, a key component of oxidative stress response. *PloS One*, *10*(6), e0129566.

A high throughput screen for compounds that induce TRAIL-mediated apoptosis identified ML100 as an active chemical probe, which potentiated TRAIL activity in prostate carcinoma PPC-1 and melanoma MDA-MB-435 cells. Follow-up in silico modeling and profiling in cell-based assays allowed us to identify NSC130362, pharmacophore analog of ML100 that induced 65-95% cytotoxicity in cancer cells and did not affect the viability of human primary hepatocytes. In agreement with the activation of the apoptotic pathway, both ML100 and NSC130362 synergistically with TRAIL induced caspase-3/7 activity in MDA-MB-435 cells. Subsequent affinity chromatography and inhibition studies convincingly demonstrated that glutathione reductase (GSR), a key component of the oxidative stress response, is a target of NSC130362. In accordance with the role of GSR in the TRAIL pathway, GSR gene silencing potentiated TRAIL activity in MDA-MB-435 cells but not in human hepatocytes. Inhibition of GSR activity resulted in the induction of oxidative stress, as was evidenced by an increase in intracellular reactive oxygen species (ROS) and peroxidation of mitochondrial membrane after NSC130362 treatment in MDA-MB-435 cells but not in human hepatocytes. The antioxidant reduced glutathione (GSH) fully protected MDA-MB-435 cells from cell lysis induced by NSC130362 and TRAIL, thereby further confirming the interplay between GSR and TRAIL. As a consequence of activation of oxidative stress, combined treatment of different oxidative stress inducers and NSC130362 promoted cell death in a variety of cancer cells but not in hepatocytes in cell-based assays and in in vivo, in a mouse tumor xenograft model.

Rudolph, S., Tsai, M. C., von Gersdorff, H., & Wadiche, J. I. (2015). The ubiquitous nature of multivesicular release. *Trends in Neurosciences*,

'Simplicity is prerequisite for reliability' (E.W. Dijkstra [1]) Presynaptic action potentials trigger the fusion of vesicles to release neurotransmitter onto postsynaptic neurons. Each release site was originally thought to liberate at most one vesicle per action potential in a probabilistic fashion, rendering synaptic transmission unreliable. However, the simultaneous release of several vesicles, or multivesicular release (MVR), represents a simple mechanism to overcome the intrinsic unreliability of synaptic transmission. MVR was initially identified at specialized synapses but is now known to be common throughout the brain. MVR determines the temporal and spatial dispersion of transmitter, controls the extent of receptor activation, and contributes to adapting synaptic strength during plasticity and neuromodulation. MVR consequently represents a widespread mechanism that extends the dynamic range of synaptic processing.

Salehi, S., Davis, H. B., Ferracane, J. L., & Mitchell, J. C. (2015). Sol-gel-derived bioactive glasses demonstrate antimicrobial effects on common oral bacteria. *American Journal of Dentistry, 28*(2), 111-115.

Purpose: To determine the antibacterial effect of nano-structured, sol-gel processed bioactive glasses that may be used for implants, coatings, and as adjuncts to dental restorative materials. Methods: Six bioactive glasses (BAG), three made with differing amounts of silica (65, 75 and 85 mole%), and three with different amounts of silica (61, 71, and 81 mole%) and 3 mole% fluoride were prepared by a sol-gel synthesis method and tested against clinically important bacteria species, Streptococcus sobrinus (ATCC33478), Streptococcus mutans (ATCC25175) and Enterococcus faecalis (ATCC19433). Bacterial suspensions were independently incubated with bioactive glass in particulate form (< 3 μm) for 4 and 24 hours. Viability was determined by colony-forming units. Results: At 4 hours, all BAG produced an order of magnitude reduction in all three bacteria. After 24 hours, all BAG produced a significant reduction in S. sobrinus colonies, but no further reduction in S. mutans; all BAG, except BAG 61-F, significantly reduced E. faecalis compared to the control. At 4 hours, an increase in the pH of the BAG groups (to pH 9) could also have contributed to the bactericidal effect. In further experiments it was found that the viability of S. sobrinus was significantly reduced following exposure to an extract of BAG in media adjusted to a pH of 7.4. Additionally media with pH adjusted to 9 exerted a significant antibacterial effect against S. sobrinus after 4 hours. To determine the influence of the calcium

ions released from the BAG in the absence of the pH effect, a typical dose response was demonstrated after 4 hours of exposure of S. sobrinus to media containing various levels of calcium. The results of this study clearly suggest that the effect of BAG extract on bacteria is not only related to a pH effect, but is also linked to an effect of liberated ions, such as calcium, extracted from the surface of the bioactive glasses.

Sayer, N. A., Orazem, R. J., Noorbaloochi, S., Gravely, A., Frazier, P., Carlson, K. F., et al. (2015). Iraq and afghanistan war veterans with reintegration problems: Differences by veterans affairs healthcare user status. *Administration and Policy in Mental Health and Mental Health Services Research*, *42*(4), 493-503.

We studied 1,292 Iraq and Afghanistan War veterans who participated in a clinical trial of expressive writing to estimate the prevalence of perceived reintegration difficulty and compare Veterans Affairs (VA) healthcare users to nonusers in terms of demographic and clinical characteristics. About half of participants perceived reintegration difficulty. VA users and nonusers differed in age and military background. Levels of mental and physical problems were higher in VA users. In multivariate analysis, military service variables and probable traumatic brain injury independently predicted VA use. Findings demonstrate the importance of research comparing VA users to nonusers to understand veteran healthcare needs. © 2014, The Author(s).

Scalco, R. C., Hwa, V., Domene, H., Jasper, H. G., Belgorosky, A., Marino, R., et al. (2015). STAT5B mutations in heterozygous state have negative impact on height: Another clue in human stature heritability. *European Journal of Endocrinology / European Federation of Endocrine Societies*, CONTEXT AND OBJECTIVE: Growth hormone insensitivity with immune dysfunction caused by signal transducer and activator of transcription 5B (STAT5B) mutations is an autosomal recessive condition. Heterozygous mutations in other genes involved in growth regulation were previously associated with a mild height reduction. Our objective was to assess for the first time the phenotype of heterozygous STAT5B mutations. METHODS: We genotyped and performed clinical and laboratorial evaluations in 52 relatives of 2 previously described Brazilian brothers with homozygous STAT5B c.424_427del mutation (21 heterozygous). Additionally, we obtained height

data and genotype from 1,104 adult control individuals from the same region in Brazil and identified 5 additional families harboring the same mutation (18 individuals, 11 heterozygous). Furthermore, we gathered the available height data from first-degree relatives of patients with homozygous STAT5B mutations (17 individuals from 7 families). Data from heterozygous individuals and non-carriers were compared. RESULTS: Individuals carrying heterozygous STAT5B c.424_427del mutation were 0.6 SDS shorter than their non-carrier relatives (p= 0.009). Heterozygous subjects also had significantly lower Z-scores for serum concentrations of IGF-1 (p=0.028) and IGFBP-3 (p=0.02) than their non-carrier relatives. The 17 heterozygous first-degree relatives of patients carrying homozygous STAT5B mutations had an average height SDS of -1.4 +/- 0.8 when compared with population-matched controls (p < 0.001). CONCLUSIONS: STAT5B mutations in heterozygous state have a significant negative impact on height (approximately 3.9 cm). This effect is milder than the effect seen in the homozygous state, with height usually within the normal range. Our results support the hypothesis that heterozygosity of rare pathogenic variants contributes to normal height heritability.

Schroll, R., Smith, A., McSwain, N. E.,Jr, Myers, J., Rocchi, K., Inaba, K., et al. (2015). A multi-institutional analysis of prehospital tourniquet use. *The Journal of Trauma and Acute Care Surgery, 79*(1), 10-14.

BACKGROUND: Recent military studies demonstrated an association between prehospital tourniquet use and increased survival. The benefits of this prehospital intervention in a civilian population remain unclear. The aims of our study were to evaluate tourniquet use in the civilian population and to compare outcomes to previously published military experience. We hypothesized that incorporation of tourniquet use in the civilian population will result in an overall improvement in mortality. METHODS: This is a preliminary multi-institutional retrospective analysis of prehospital tourniquet (MIA-T) use of patients admitted to nine urban Level 1 trauma centers from January 2010 to December 2013. Patient demographics and mortality from a previous military experience by Kragh et al. (Ann Surg. 2009;249:1-7) were used for comparison. Patients younger than 18 years or with nontraumatic bleeding requiring tourniquet application were excluded. Data were analyzed using a two-tailed unpaired Student's t test with p < 0.05 as significant. RESULTS: A total of 197 patients were included. Tourniquets were applied

effectively in 175 (88.8%) of 197 patients. The average Injury Severity Score (ISS) for MIA-T versus military was 11 +/- 12.5 versus 14 +/- 10.5, respectively (p = 0.02). The overall mortality and limb amputation rates for the MIA-T group were significantly lower than previously seen in the military population at 6 (3.0%) of 197 versus 22 (11.3%) of 194 (p = 0.002) and 37 (18.8%) of 197 versus 97 (41.8%) of 232 (p = 0.0001), respectively. CONCLUSION: Our study is the largest evaluation of prehospital tourniquet use in a civilian population to date. We found that tourniquets were applied safely and effectively in the civilian population. Adaptation of this prehospital intervention may convey a survival benefit in the civilian population. LEVEL OF EVIDENCE: Epidemiologic study, level V.

Schulze-Späte, U., Turner, R., Wang, Y., Chao, R., Schulze, P. C., Phipps, K., et al. (2015). Relationship of bone metabolism biomarkers and periodontal disease: The osteoporotic fractures in men (MrOS) study. *Journal of Clinical Endocrinology and Metabolism*, *100*(6), 2425-2433. Context: Periodontitis is an inflammatory disease of tooth-supporting tissue leading to bone destruction and tooth loss. Periodontitis affects almost 50% of adults greater than 30 years of age. Objective: This study evaluated the association between biomarkers linked to bone formation and resorption with the occurrence and progression of periodontal disease in older men (≥65 y). Design: The Osteoporotic Fractures in Men (MrOS) study is a prospective, observational study among men 65 years of age and older. Setting: This ancillary study, Oral and Skeletal Bone Loss in Older Men, was conducted at two of the six MrOS study sites (Birmingham, AL and Portland, OR). Patients: Patients underwent medical and dental evaluation. Diagnoses of periodontitis were based on clinical attachment loss, pocket depth, calculus, plaque, and bleeding on a random half-mouth. Bone metabolism biomarkers included serum levels of calcium, phosphate (Pi), alkaline phosphatase, albumin, carboxy-terminal collagen crosslinks (CTX), N-terminal propeptides of type I procollagen, isoform 5b of tartrate-resistant acid phosphatase, and urine alpha- carboxyterminal collagen crosslinks (alpha-CTX) and beta-CTX and serum levels of calciotropic hormones vitamin D (25(OH)D) and PTH. Main Outcome Measures: The aim of this study is to correlate bone metabolism biomarkers with prevalence and progression of periodontal disease in older men. Results: Patients with more severe periodontitis had significantly higher levels of PTH (P trend = .0004), whereas 25(OH)D was lower (P trend = .001). In a subset of

men reevaluated at a second dental visit, improvement of periodontitis was associated with lower alpha-CTX, beta-CTX, and CTX levels at baseline after adjusting for age, site, and body mass index. Conclusion: This study suggests that a distinct set of biomarkers of bone metabolism are associated with more severe periodontal disease (PTH, 25(OH)D) and periodontal progression (alpha-CTX, beta-CTX, and CTX) over time. Copyright © 2015 by the Endocrine Society.

Seamon, M. J., Haut, E. R., Van Arendonk, K., Barbosa, R. R., Chiu, W. C., Dente, C. J., et al. (2015). An evidence-based approach to patient selection for emergency department thoracotomy: A practice management guideline from the eastern association for the surgery of trauma. *The Journal of Trauma and Acute Care Surgery, 79*(1), 159-173.

BACKGROUND: Within the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework, we performed a systematic review and developed evidence-based recommendations to answer the following PICO (Population, Intervention, Comparator, Outcomes) question: should patients who present pulseless after critical injuries (with and without signs of life after penetrating thoracic, extrathoracic, or blunt injuries) undergo emergency department thoracotomy (EDT) (vs. resuscitation without EDT) to improve survival and neurologically intact survival? METHODS: All patients who underwent EDT were included while those involving either prehospital resuscitative thoracotomy or operating room thoracotomy were excluded. Quantitative synthesis via meta-analysis was not possible because no comparison or control group (i.e., survival or neurologically intact survival data for similar patients who did not undergo EDT) was available for the PICO questions of interest. RESULTS: The 72 included studies provided 10,238 patients who underwent EDT. Patients presenting pulseless after penetrating thoracic injury had the most favorable EDT outcomes both with (survival, 182 [21.3%] of 853; neurologically intact survival, 53 [11.7%] of 454) and without (survival, 76 [8.3%] of 920; neurologically intact survival, 25 [3.9%] of 641) signs of life. In patients presenting pulseless after penetrating extrathoracic injury, EDT outcomes were more favorable with signs of life (survival, 25 [15.6%] of 160; neurologically intact survival, 14 [16.5%] of 85) than without (survival, 4 [2.9%] of 139; neurologically intact survival, 3 [5.0%] of 60). Outcomes after EDT in pulseless blunt injury patients were limited with signs of life (survival, 21 [4.6%] of 454; neurologically intact survival, 7 [2.4%] of 298) and dismal without signs of life

(survival, 7 [0.7%] of 995; neurologically intact survival, 1 [0.1%] of 825). CONCLUSION: We strongly recommend that patients who present pulseless with signs of life after penetrating thoracic injury undergo EDT. We conditionally recommend EDT for patients who present pulseless and have absent signs of life after penetrating thoracic injury, present or absent signs of life after penetrating extrathoracic injury, or present signs of life after blunt injury. Lastly, we conditionally recommend against EDT for pulseless patients without signs of life after blunt injury. LEVEL OF EVIDENCE: Systematic review/guideline, level III.

Seifer, D. B., & Tal, R. (2015). Personalized prediction of live birth: Are we there yet? *Fertility and Sterility*,

Shapiro, E. G., Nestrasil, I., Rudser, K., Delaney, K., Kovac, V., Ahmed, A., et al. (2015). Neurocognition across the spectrum of mucopolysaccharidosis type I: Age, severity, and treatment. *Molecular Genetics and Metabolism*,

OBJECTIVES: Precise characterization of cognitive outcomes and factors that contribute to cognitive variability will enable better understanding of disease progression and treatment effects in mucopolysaccharidosis type I (MPS I). We examined the effects on cognition of phenotype, genotype, age at evaluation and first treatment, and somatic disease burden. METHODS: Sixty patients with severe MPS IH (Hurler syndrome treated with hematopoietic cell transplant and 29 with attenuated MPS I treated with enzyme replacement therapy), were studied with IQ measures, medical history, genotypes. Sixty-seven patients had volumetric MRI. Subjects were grouped by age and phenotype and MRI and compared to 96 normal controls. RESULTS: Prior to hematopoietic cell transplant, MPS IH patients were all cognitively average, but post-transplant, 59% were below average, but stable. Genotype and age at HCT were associated with cognitive ability. In attenuated MPS I, 40% were below average with genotype and somatic disease burden predicting their cognitive ability. White matter volumes were associated with IQ for controls, but not for MPS I. Gray matter volumes were positively associated with IQ in controls and attenuated MPS I patients, but negatively associated in MPS IH. CONCLUSIONS: Cognitive impairment, a major difficulty for many MPS I patients, is associated with genotype, age at treatment and somatic disease burden. IQ association with white matter differed from controls. Many attenuated

MPS patients have significant physical and/or cognitive problems and receive insufficient support services. Results provide direction for future clinical trials and better disease management.

She, H., Chen, R. -., Dibella, E. V. R., Schabel, M., & Ying, L. (2014). Highly accelerated dynamic contrast-enhanced MRI with temporal constrained reconstruction. *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014*, pp. 2408-2411.
For DCE MRI applications, the images of adjacent time frames are often similar, especially when motion is minimal, in which case temporal TV is a reasonable regularization term. Temporal constraint reconstruction (TCR) has been developed to reconstruct dynamic images from undersampled k-t space data based on such prior information. However, the convergence speed of the algorithm highly depends on the initialization method. In this study, we study initialization using a composite high resolution image based on a jigsaw sampling pattern during pre-contrast frames. The proposed initialization method converges much faster than a conventional initialization method using low resolution images, especially at high reduction factors. In vivo breast imaging experiments were carried out to evaluate the performance of the proposed method. Experiments show the new initialization method allows TCR to achieve a high reduction factor up to 40 without compromising much of the spatial or temporal resolution. The reconstruction errors are much lower than those using the low resolution initialization when the same number of measurements is used.

Simmons, K. B., & Edelman, A. B. (2015). Contraception and sexual health in obese women. *Best Practice and Research: Clinical Obstetrics and Gynaecology, 29*(4), 466-478.
As the proportion of women with obesity increases worldwide, understanding the influence of body weight on sexual behavior, fertility, and contraceptive effectiveness is critical for health-care professionals and patients. Although many have theorized that obese women are different from normal-weight women regarding sexual health and behavior, current evidence for the most part disproves this. The exception is in adolescents where body image may play a role in riskier behavior, placing them at a greater risk of an unintended pregnancy. Given that most modern contraceptives were not originally evaluated in obese women, understanding how weight affects contraceptive pharmacokinetics and efficacy should be a focus of ongoing research. Evidence is

reassuring that most modern contraceptive methods are safe and effective in obese women. This paper reviews what is known about sexual and contraceptive behavior, as well as the effectiveness and pharmacokinetics of modern contraceptives, for overweight and obese women. © 2014 Elsevier Ltd. All rights reserved.

Simmons, K. B., & Rodriguez, M. I. (2015). Reducing unintended pregnancy through provider training. *Lancet (London, England)*,

Simpson, E. L., Williams, H., & Chalmers, J. (2015). Reply. *The Journal of Allergy and Clinical Immunology*, *135*(6), 1664.

Sista, A. K., Vedantham, S., Kaufman, J. A., & Madoff, D. C. (2015). Endovascular interventions for acute and chronic lower extremity deep venous disease: State of the art. *Radiology*, *276*(1), 31-53.

The societal and individual burden caused by acute and chronic lower extremity venous disease is considerable. In the past several decades, minimally invasive endovascular interventions have been developed to reduce thrombus burden in the setting of acute deep venous thrombosis to prevent both short- and long-term morbidity and to recanalize chronically occluded or stenosed postthrombotic or nonthrombotic veins in symptomatic patients. This state-of-the-art review provides an overview of the techniques and challenges, rationale, patient selection criteria, complications, postinterventional care, and outcomes data for endovascular intervention in the setting of acute and chronic lower extremity deep venous disease. Online supplemental material is available for this article. ((c)) RSNA, 2015.

Skubic, M., Jimison, H., Keller, J., Popescu, M., Rantz, M., Kaye, J., et al. (2014). A framework for harmonizing sensor data to support embedded health assessment. *2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014*, pp. 1747-1751.

The use of in-home and mobile sensing is likely to be a key component of future care and has recently been studied by many research groups world-wide. Researchers have shown that embedded sensors can be used for health assessment such as early illness detection and the

management of chronic health conditions. However, research collaboration and data sharing have been hampered by disparate sets of sensors and data collection methods. To date, there have been no studies to investigate common measures that can be used across multiple sites with different types of sensors, which would facilitate large scale studies and reuse of existing datasets. In this paper, we propose a framework for harmonizing heterogeneous sensor data through an intermediate layer, the Conceptual Sensor, which maps physical measures to clinical space. Examples are included for sleep quality and ambulatory physical function. © 2014 IEEE.

Sonnenberg, A., & Genta, R. M. (2015). Epithelial dysplasia and cancer in IBD strictures. *Journal of Crohn's & Colitis*,

BACKGROUND: The presence of colonic strictures and epithelial dysplasia are both known risk factors for the occurrence of colorectal cancer in IBD patients. The aim of the present report was to study the risk of colonic stricture for the occurrence of epithelial dysplasia and colonic adenocarcinoma. METHODS: In a case-control study among 53,568 IBD patients undergoing colonoscopy, we compared the prevalence of strictures among cases with dysplasia or adenocarcinoma and controls without such complications by calculating odds ratios (OR) and their 95% confidence intervals (CI). Multivariate logistic regressions were used to assess the joint influence of multiple predictor variables (age, sex, IBD type, and stricture) on the occurrence of colonic dysplasia or adenocarcinoma. RESULTS: The prevalence of strictures was 1.06% in ulcerative colitis (UC) and 8.71% in Crohn's disease (CD, OR 11.09, CI 9.72-12.70). The prevalence of dysplasia was 3.22% in UC and 2.08% in CD (OR = 0.75, 0.65-0.86). The prevalence of dysplasia was similar in IBD patients with and without stricture: 2.82% vs. 2.41%, respectively. The prevalence of cancer was higher in IBD patients with than without stricture: 0.78% vs. 0.11%, respectively (OR = 6.87, 3.30-12.89). In the multivariate analysis, old age, male sex, and UC, but not stricture, were all significantly and independently associated with dysplasia. Old age, dysplasia, and stricture were significantly and independently associated with cancer. CONCLUSION: The prevalence of epithelial dysplasia is not generally increased in IBD patients with strictures.

Spinelli, K. J., Osterberg, V. R., Meshul, C. K., Soumyanath, A., & Unni, V. K. (2015). Curcumin treatment improves motor behavior in alpha-synuclein transgenic mice. *PloS One, 10*(6), e0128510.

The curry spice curcumin plays a protective role in mouse models of neurodegenerative diseases, and can also directly modulate aggregation of alpha-synuclein protein in vitro, yet no studies have described the interaction of curcumin and alpha-synuclein in genetic synucleinopathy mouse models. Here we examined the effect of chronic and acute curcumin treatment in the Syn-GFP mouse line, which overexpresses wild-type human alpha-synuclein protein. We discovered that curcumin diet intervention significantly improved gait impairments and resulted in an increase in phosphorylated forms of alpha-synuclein at cortical presynaptic terminals. Acute curcumin treatment also caused an increase in phosphorylated alpha-synuclein in terminals, but had no direct effect on alpha-synuclein aggregation, as measured by in vivo multiphoton imaging and Proteinase-K digestion. Using LC-MS/MS, we detected ~5 ng/mL and ~12 ng/mL free curcumin in the plasma of chronic or acutely treated mice, with a glucuronidation rate of 94% and 97%, respectively. Despite the low plasma levels and extensive metabolism of curcumin, these results show that dietary curcumin intervention correlates with significant behavioral and molecular changes in a genetic synucleinopathy mouse model that mimics human disease.

Sripada, R. K., Bohnert, A. S. B., Teo, A. R., Levine, D. S., Pfeiffer, P. N., Bowersox, N. W., et al. (2015). Social networks, mental health problems, and mental health service utilization in OEF/OIF national guard veterans. *Social Psychiatry and Psychiatric Epidemiology*,

Purpose: Low social support and small social network size have been associated with a variety of negative mental health outcomes, while their impact on mental health services use is less clear. To date, few studies have examined these associations in National Guard service members, where frequency of mental health problems is high, social support may come from military as well as other sources, and services use may be suboptimal. Methods: Surveys were administered to 1448 recently returned National Guard members. Multivariable regression models assessed the associations between social support characteristics, probable mental health conditions, and service utilization. Results: In bivariate analyses, large social network size, high social network diversity, high perceived social support, and high military unit support were each associated with

lower likelihood of having a probable mental health condition ($p < .001$). In adjusted analyses, high perceived social support (OR .90, CI .88–.92) and high unit support (OR .96, CI .94–.97) continued to be significantly associated with lower likelihood of mental health conditions. Two social support measures were associated with lower likelihood of receiving mental health services in bivariate analyses, but were not significant in adjusted models. Conclusions: General social support and military-specific support were robustly associated with reduced mental health symptoms in National Guard members. Policy makers, military leaders, and clinicians should attend to service members' level of support from both the community and their units and continue efforts to bolster these supports. Other strategies, such as focused outreach, may be needed to bring National Guard members with need into mental health care.

St George, R., Carlson-Kuhta, P., King, L. A., Burchiel KJ, D., & Horak, F. B. (2015). Compensatory stepping in parkinson's disease is still a problem after deep brain stimulation randomized to STN or GPi. *Journal of Neurophysiology*, , jn.01052.2014.

The effects of Deep Brain Stimulation (DBS) on balance in people with Parkinson's Disease (PD) are not well established. This study examined whether DBS randomized to the subthalamic nucleus (STN, n=11) or globus pallidus interna (GPi, n=10) improved compensatory stepping to recover balance following a perturbation. The standing surface translated backwards, forcing subjects to take compensatory steps forward. Kinematic and kinetic responses were recorded. PD-DBS subjects were tested off and on their levodopa medication before bilateral DBS surgery, and retested six months later off and on DBS, combined with off and on levodopa medication. Responses were compared with PD-control subjects (n=8) tested over the same time scale and 17 healthy control subjects. Neither DBS nor levodopa improved the stepping response. Compensatory stepping in the best-treated state after surgery (DBS+DOPA) was similar to the best-treated state before surgery (DOPA) for the PD-GPi group and the PD control group. For the PD-STN group, there were more lateral weight shifts, a delayed foot-off and a greater number of steps required to recover balance in DBS+DOPA after surgery, compared to DOPA before surgery. Within the STN group, 5 subjects who did not fall during the experiment before surgery fell at least once after surgery, whereas the number of falls in the GPi and PD-control groups were

unchanged. DBS did not improve the compensatory step response needed to recover from balance perturbations in the GPi group and caused delays in the preparation phase of the step in the STN group.

Stephenson, K., & Rosen, D. H. (2015). Haiku and healing: An empirical study of poetry writing as therapeutic and creative intervention. *Empirical Studies of the Arts, 33*(1), 36-60.

Haiku poetry was investigated in the context of the expressive writing paradigm to evaluate its potential benefits. Participants, 98 introductory psychology students at a large southwestern university, wrote for 20 min a day on 3 consecutive days and completed self-report measures of happiness, life satisfaction, spiritual meaning, creativity, physiological symptomatology, depression, anxiety, and health/illness orientation at baseline and 3-week follow-up. A series of analysis of covariance linear contrasts were used to examine differences between groups writing narrative about a neutral topic, haiku about a neutral topic, haiku about nature, or haiku about a negative life event. Writing in narrative about a neutral topic led to decreases in anxiety and depression. Participants writing haiku about nature or a negative life event reported increased creativity, and writing haiku about nature led to decreased illness orientation. The present findings suggest that narrative writing leads to decreases in anxiety and depression, while haiku writing increases creativity and sensitivity to topic. The value of haiku and the arts are discussed for the writing paradigm and beyond. © The Author(s) 2015.

Stincic, T. L., & Frerking, M. E. (2015). Different AMPA receptor subtypes mediate the distinct kinetic components of a biphasic EPSC in hippocampal interneurons. *Frontiers in Synaptic Neuroscience, 7*, 7.

CA1 hippocampal interneurons at the border between stratum radiatum (SR) and stratum lacunosum-moleculare (SLM) have AMPA receptor (AMPAR)-mediated excitatory postsynaptic currents (EPSCs) that consist of two distinct phases: a typical fast component (FC), and a highly unusual slow component (SC) that persists for hundreds of milliseconds. To determine whether these kinetically distinct components of the EPSC are mediated by distinct AMPAR subpopulations, we examined the relative contributions of GluA2-containing and-lacking AMPARs to the SC. GluA2-containing AMPARs mediated the majority of the FC whereas GluA2-lacking

AMPARs preferentially generated the SC. When glutamate uptake through the glial glutamate transporter excitatory amino acid transporter (EAAT1) was inhibited, spill over-mediated AMPAR activation recruited an even slower third kinetic component that persisted for several seconds; however, this spillover-mediated current was mediated predominantly by GluA2-containing AMPARs and therefore was clearly distinct from the SC when uptake is intact. Thus, different AMPAR subpopulations that vary in GluA2 content mediate the distinct components of the AMPAR EPSC. The SC is developmentally downregulated in mice, declining after the second postnatal week. This downregulation affects both GluA2-containing and GluA2-lacking AMPARs mediating the SC, and is not accompanied by developmental changes in the GluA2 content of AMPARs underlying the FC. Thus, the downregulation of the SC appears to be independent of synaptic GluA2 expression, suggesting the involvement of another AMPAR subunit or an auxiliary protein. Our results therefore identify GluA2-dependent and GluA2-independent determinants of the SC: GluA2-lacking AMPARs preferentially contribute to the SC, while the developmental downregulation of the SC is independent of GluA2 content.

Storzbach, D., O'Neil, M. E., Roost, S. -., Kowalski, H., Iverson, G. L., Binder, L. M., et al. (2015). Comparing the neuropsychological test performance of operation enduring Freedom/Operation iraqi freedom (OEF/OIF) veterans with and without blast exposure, mild traumatic brain injury, and posttraumatic stress symptoms. *Journal of the International Neuropsychological Society*,
To compare neuropsychological test performance of Veterans with and without mild traumatic brain injury (MTBI), blast exposure, and posttraumatic stress disorder (PTSD) symptoms. We compared the neuropsychological test performance of 49 Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans diagnosed with MTBI resulting from combat blast-exposure to that of 20 blast-exposed OEF/OIF Veterans without history of MTBI, 23 OEF/OIF Veterans with no blast exposure or MTBI history, and 40 matched civilian controls. Comparison of neuropsychological test performance across all four participant groups showed a complex pattern of mixed significant and mostly nonsignificant results, with omnibus tests significant for measures of attention, spatial abilities, and executive function. The most consistent pattern was the absence of significant differences between blast-exposed Veterans with MTBI history and blast-exposed Veterans without MTBI history. When blast-exposed Veteran groups with and without

MTBI history were aggregated and compared to non–blast-exposed Veterans, there were significant differences for some measures of learning and memory, spatial abilities, and executive function. However, covariation for severity of PTSD symptoms eliminated all significant omnibus neuropsychological differences between Veteran groups. Our results suggest that, although some mild neurocognitive effects were associated with blast exposure, these neurocognitive effects might be better explained by PTSD symptom severity rather than blast exposure or MTBI history alone. (JINS, 2015, 21, 1–11) Copyright © The International Neuropsychological Society 2015

Stuve, O., & Bourdette, D. (2015). Natalizumab to fingolimod: Questions answered, unanswered, and unasked. *Neurology*,

Subak, L. L., King, W. C., Belle, S. H., Chen, J. Y., Courcoulas, A. P., Ebel, F. E., et al. (2015). Urinary incontinence before and after bariatric surgery. *JAMA Internal Medicine*,
Importance: Among women and men with severe obesity, evidence for improvement in urinary incontinence beyond the first year after bariatric surgery-induced weight loss is lacking. Objectives: To examine change in urinary incontinence before and after bariatric surgery and to identify factors associated with improvement and remission among women and men in the first 3 years after bariatric surgery. Design, Setting, and Participants: The Longitudinal Assessment of Bariatric Surgery 2 is an observational cohort study at 10 US hospitals in 6 geographically diverse clinical centers. Participants were recruited between February 21, 2005, and February 17, 2009. Adults undergoing first-time bariatric surgical procedures as part of clinical care by participating surgeons between March 14, 2006, and April 24, 2009, were followed up for 3 years (through October 24, 2012). Intervention: Participants undergoing bariatric surgery completed research assessments before the procedure and annually thereafter. Main Outcomes and Measures: The frequency and type of urinary incontinence episodes in the past 3 months were assessed using a validated questionnaire. Prevalent urinary incontinence was defined as at least weekly urinary incontinence episodes, and remission was defined as change from prevalent urinary incontinence at baseline to less than weekly urinary incontinence episodes at follow-up. Results: Of 2458 participants, 1987 (80.8%) completed baseline and follow-up assessments. At baseline, the median age was 47 years (age range, 18-78 years), the median body mass index was 46 kg/m2

(range, 34-94 kg/m2), and 1565 of 1987 (78.8%) were women. Urinary incontinence was more prevalent among women (49.3%; 95% CI, 46.9%-51.9%) than men (21.8%; 95% CI, 18.2%-26.1%) (P < .001). After a mean 1-year weight loss of 29.5% (95% CI, 29.0%-30.1%) in women and 27.0% (95% CI, 25.9%-28.6%) in men, year 1 urinary incontinence prevalence was significantly lower among women (18.3%; 95% CI, 16.4%-20.4%) and men (9.8%; 95% CI, 7.2%-13.4%) (P < .001 for all). The 3-year prevalence was higher than the 1-year prevalence for both sexes (24.8%; 95% CI, 21.8%-26.5% among women and 12.2%; 95% CI, 9.0%-16.4% among men) but was substantially lower than baseline (P < .001 for all). Weight loss was independently related to urinary incontinence remission (relative risk, 1.08; 95% CI, 1.06-1.10 in women and 1.07; 95% CI, 1.02-1.13 in men) per 5% weight loss, as were younger age and the absence of a severe walking limitation. Conclusions and Relevance: Among women and men with severe obesity, bariatric surgery was associated with substantially reduced urinary incontinence over 3 years. Improvement in urinary incontinence may be an important benefit of bariatric surgery.

Sukumar, M. (2014). *Transcervical thymectomy and extended thymectomy with bilateral opening of the mediastinal pleura* Springer-Verlag Berlin Heidelberg.

Transcervical thymectomy is a now well-established procedure for thymectomy in patients with myasthenia gravis. Transcervical video-assisted extended thymectomy can be performed safely and with minimal morbidity.

Sullivan, D. R., Golden, S. E., Ganzini, L., Hansen, L., & Slatore, C. G. (2015). 'I still don't know diddly': A longitudinal qualitative study of patients' knowledge and distress while undergoing evaluation of incidental pulmonary nodules. *NPJ Primary Care Respiratory Medicine*, *25*, 15028.

BACKGROUND: Hundreds of thousands of incidental pulmonary nodules are detected annually in the United States, and this number will increase with the implementation of lung cancer screening. The lengthy period for active pulmonary nodule surveillance, often several years, is unique among cancer regimens. The psychosocial impact of longitudinal incidental nodule follow-up, however, has not been described. AIMS: We sought to evaluate the psychosocial impact of longitudinal follow-up of incidental nodule detection on patients. METHODS: Veterans who

participated in our previous study had yearly follow-up qualitative interviews coinciding with repeat chest imaging. We used conventional content analysis to explore their knowledge of nodules and the follow-up plan, and their distress. RESULTS: Seventeen and six veterans completed the year one and year two interviews, respectively. Over time, most patients continued to have inadequate knowledge of pulmonary nodules and the nodule follow-up plan. They desired and appreciated more information directly from their primary care provider, particularly about their lung cancer risk. Distress diminished over time for most patients, but it increased around the time of follow-up imaging for some, and a small number reported severe distress. CONCLUSIONS: In settings in which pulmonary nodules are commonly detected, including lung cancer screening programmes, resources to optimise patient-centred communication strategies that improve patients' knowledge and reduce distress should be developed.

Sun, H., Yedinak, C., Ozpinar, A., Anderson, J., Dogan, A., Delashaw, J., et al. (2015). Preoperative lateralization modalities for cushing disease: Is dynamic magnetic resonance imaging or cavernous sinus sampling more predictive of intraoperative findings? *Journal of Neurological Surgery, Part B: Skull Base, 76*(3), 218-224.

Objective To analyze whether cavernous sinus sampling (CSS) and dynamic magnetic resonance imaging (dMRI) are consistent with intraoperative findings in Cushing disease (CD) patients. Design Retrospective outcomes study. Setting Oregon Health & Science University; 2006 and 2013. Participants A total of 37 CD patients with preoperative dMRI and CSS to confirm central adrenocorticotropic hormone (ACTH) hypersecretion. Patients were 78% female; mean age was 41 years (at diagnosis), and all had a minimum of 6 months of follow-up. Main Outcome Measures Correlations among patient characteristics, dMRI measurements, CSS results, and intraoperative findings. Results All CSS indicated presence of CD. Eight of 37 patients had no identifiable tumor on dMRI. Three of 37 patients had no tumor at surgery. dMRI tumor size was inversely correlated with age (rs=- 0.4; p=0.01) and directly correlated to intraoperative lateralization (rs=0.3; p<0.05). Preoperative dMRI was directly correlated to intraoperative lateralization (rs=0.5; p<0.002). CSS lateralization showed no correlation with intraoperative findings (rs=0.145; p=0.40) or lateralization observed on preoperative dMRI (rs=0.17; p=0.29).

Postoperative remission rate was 68%. Conclusion dMRI localization was most consistent with intraoperative findings; CSS results were less reliable. Results suggest that small ACTH-secreting tumors continue to pose a challenge to reliable preoperative localization. © 2015 Georg Thieme Verlag KG Stuttgart . New York.

Tal, R., Seifer, D. B., & Arici, A. (2015). The emerging role of angiogenic factor dysregulation in the pathogenesis of polycystic ovarian syndrome. *Seminars in Reproductive Medicine*, *33*(3), 195-207.

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder in reproductive age affecting 5 to 7% of women. It is characterized by anovulatory infertility, hyperandrogenism, and polycystic ovaries. Angiogenesis in the ovary is critical for follicular growth, ovulation, and the subsequent development and regression of the corpus luteum. Accumulating evidence suggests that multiple angiogenic factors are dysregulated in PCOS, including vascular endothelial growth factor, angiopoietins, platelet-derived growth factor, transforming growth factor-beta, and basic fibroblast growth factor. This angiogenic factor imbalance likely underlies the increased stromal vascularity observed in PCOS. Angiogenic factor dysregulation may play an important role in the pathophysiology of PCOS and may contribute to ovulatory dysfunction, subfertility, and ovarian hyperstimulation syndrome, which are commonly seen in women with PCOS. Further experimental studies are needed to gain a better understanding of the growth factors that are involved in normal and pathological ovarian angiogenesis, and to assess the potential of angiogenesis-based treatment strategies in PCOS.

Tallino, S., Duffy, M., Ralle, M., Cortes, M. P., Latorre, M., & Burkhead, J. L. (2015). Nutrigenomics analysis reveals that copper deficiency and dietary sucrose up-regulate inflammation, fibrosis and lipogenic pathways in a mature rat model of nonalcoholic fatty liver disease. *The Journal of Nutritional Biochemistry*,

Nonalcoholic fatty liver disease (NAFLD) prevalence is increasing worldwide, with the affected US population estimated near 30%. Diet is a recognized risk factor in the NAFLD spectrum, which includes nonalcoholic steatohepatitis (NASH) and fibrosis. Low hepatic copper (Cu) was recently linked to clinical NAFLD/NASH severity. Simple sugar consumption including sucrose and fructose

is implicated in NAFLD, while consumption of these macronutrients also decreases liver Cu levels. Though dietary sugar and low Cu are implicated in NAFLD, transcript-level responses that connect diet and pathology are not established. We have developed a mature rat model of NAFLD induced by dietary Cu deficiency, human-relevant high sucrose intake (30% w/w) or both factors in combination. Compared to the control diet with adequate Cu and 10% (w/w) sucrose, rats fed either high-sucrose or low-Cu diet had increased hepatic expression of genes involved in inflammation and fibrogenesis, including hepatic stellate cell activation, while the combination of diet factors also increased ATP citrate lyase and fatty acid synthase gene transcription (fold change >2, P<0.02). Low dietary Cu decreased hepatic and serum Cu (P</=0.05), promoted lipid peroxidation and induced NAFLD-like histopathology, while the combined factors also induced fasting hepatic insulin resistance and liver damage. Neither low Cu nor 30% sucrose in the diet led to enhanced weight gain. Taken together, transcript profiles, histological and biochemical data indicate that low Cu and high sucrose promote hepatic gene expression and physiological responses associated with NAFLD and NASH, even in the absence of obesity or severe steatosis.

Tan, W. C., Sin, D. D., Bourbeau, J., Hernandez, P., Chapman, K. R., Cowie, R., et al. (2015). Characteristics of COPD in never-smokers and ever-smokers in the general population: Results from the CanCOLD study. *Thorax*,

BACKGROUND: There is limited data on the risk factors and phenotypical characteristics associated with spirometrically confirmed COPD in never-smokers in the general population. AIMS: To compare the characteristics associated with COPD by gender and by severity of airway obstruction in never-smokers and in ever-smokers. METHOD: We analysed the data from 5176 adults aged 40 years and older who participated in the initial cross-sectional phase of the population-based, prospective, multisite Canadian Cohort of Obstructive Lung Disease study. Never-smokers were defined as those with a lifetime exposure of <1/20 pack year. Logistic regressions were constructed to evaluate associations for 'mild' and 'moderate-severe' COPD defined by FEV1/FVC <5th centile (lower limits of normal). Analyses were performed using SAS V.9.1 (SAS Institute, Cary, North Carolina, USA). RESULTS: The prevalence of COPD (FEV1/FVC<lower limits of normal) in never-smokers was 6.4%, constituting 27% of all COPD

subjects. The common independent predictors of COPD in never-smokers and ever-smokers were older age, self reported asthma and lower education. In never-smokers a history of hospitalisation in childhood for respiratory illness was discriminative, while exposure to passive smoke and biomass fuel for heating were discriminative for women. COPD in never-smokers and ever-smokers was characterised by increased respiratory symptoms, 'respiratory exacerbation' events and increased residual volume/total lung capacity, but only smokers had reduced DLCO/Va and emphysema on chest CT scans. CONCLUSIONS: The study confirmed the substantial burden of COPD among never-smokers, defined the common and gender-specific risk factors for COPD in never-smokers and provided early insight into potential phenotypical differences in COPD between lifelong never-smokers and ever-smokers. TRIAL REGISTRATION NUMBER: NCT00920348 (ClinicalTrials.gov); study ID number: IRO-93326.

Tang, M., Li, Y., & Huang, D. (2015). Corneal epithelial remodeling after LASIK measured by fourier-domain optical coherence tomography. *Journal of Ophthalmology, 2015*, 860313.

Purpose. To quantify corneal epithelial thickness changes after myopic LASIK by OCT. Methods. Epithelial thickness before and after myopic LASIK were measured by a Fourier-domain OCT system. Average central (within 1 mm diameter) and paracentral epithelial thickness (5~6 mm diameter) before and after LASIK were compared. Correlation between central epithelial thickness change and laser spherical equivalent setting was evaluated. An epithelial smoothing constant was estimated based on a mathematical model published previously. Results. Nineteen eyes from 11 subjects were included in the study. Eyes had myopic LASIK ranging from -1.69 D to -6.75 D spherical equivalent. The average central epithelial thickness was 52.6 +/- 4.1 mum before LASIK and 56.2 +/- 4.3 mum 3 months after LASIK ($p = 0.002$). The average paracentral epithelial thickness was 51.6 +/- 6.6 mum before LASIK and 54.8 +/- 4.3 mum 3 months after LASIK ($p = 0.007$). The change in average central epithelial thickness was correlated with laser spherical equivalent ($R (2) = 0.40$, $p = 0.028$). The epithelial smoothing constant was estimated to be 0.46 mm. Conclusions. Corneal epithelial thickens centrally and paracentrally after myopic LASIK. The extent of epithelial remodeling correlated with the amount of LASIK correction and could be predicted by a mathematical model.

Tao, H., Yancey, P. G., Babaev, V. R., Blakemore, J. L., Zhang, Y., Ding, L., et al. (2015). Macrophage SR-BI mediates efferocytosis via Src/PI3K/Rac1 signaling and reduces atherosclerotic lesion necrosis. *Journal of Lipid Research*,

Macrophage apoptosis and efferocytosis are key determinants of atherosclerotic plaque inflammation and necrosis. Bone marrow transplantation studies in ApoE and LDLR deficient mice revealed that hematopoietic SR-BI deficiency results in severely defective efferocytosis in mouse atherosclerotic lesions, resulting in 17-fold higher ratio of free to macrophage-associated dead cells in lesions containing SR-BI-/- cells, 5-fold more necrosis, 65.2% less lesional collagen content, nearly 7-fold higher dead cell accumulation, and 2-fold larger lesion area. Hematopoietic SR-BI-/- deletion elicited a maladaptive inflammatory response (higher IL-1Beta, IL-6 and TNF-alpha, lower IL-10 and TGF-Beta. Efferocytosis of apoptotic thymocytes was reduced by 64% in SR-BI-/- versus WT macrophages, both in vitro and in vivo. In response to apoptotic cells, macrophage SR-BI bound with phosphatidylserine and induced Src phosphorylation and cell membrane recruitment, which led to downstream activation of PI3K and Rac1 for engulfment and clearance of apoptotic cells, as inhibition of Src decreased PI3K, Rac1-GTP, and efferocytosis in WT cells. Pharmacological inhibition of Rac1 reduced macrophage efferocytosis in a SR-BI dependent fashion, and activation of Rac1 corrected the defective efferocytosis in SR-BI-/- macrophages. Thus, deficiency of macrophage SR-BI promotes defective efferocytosis signaling via the Src/PI3K/Rac1 pathway, resulting in increased plaque size, necrosis, and inflammation.

Tedford, C. E., DeLapp, S., Jacques, S., & Anders, J. (2015). Re: "quantitative analysis of transcranial and intraparenchymal light penetration in human cadaver brain tissue" lasers in surgery and medicine, 2015;47(4):312-322. *Lasers in Surgery and Medicine*, *47*(5), 466.

Thomas, C. R.,Jr, Bonner, J. A., Hahn, S. M., Lawrence, T. S., Liu, F. F., Formenti, S. C., et al. (2015). Society of chairs of academic radiation oncology programs-endorsed radiation oncology department review process. *International Journal of Radiation Oncology, Biology, Physics*, *92*(3), 536-539.

Tilden, E. L., Lee, V. R., Allen, A. J., Griffin, E. E., & Caughey, A. B. (2015). Cost-effectiveness analysis of latent versus active labor hospital admission for medically low-risk, term women. *Birth*

(Berkeley, Calif.),

OBJECTIVE: To assess the outcomes and costs of hospital admission during the latent versus active phase of labor. Latent labor hospital admission has been consistently associated with elevated maternal risk for increased interventions, including epidural anesthesia and cesarean delivery, longer hospital stay, and higher utilization of hospital resources. METHODS: A cost-effectiveness model was built to simulate a theoretic cohort of 3.2 million term, medically low-risk women either being admitted in latent labor (/= 4 cm dilation). Outcomes included epidural use, mode of delivery, stillbirth, maternal death, and costs of care. All probability, cost, and utility estimates were derived from the literature, and total quality-adjusted life years were calculated. Sensitivity analyses and a Monte Carlo simulation were used to investigate the robustness of model assumptions. RESULTS: Delaying admission until active labor would result in 672,000 fewer epidurals, 67,232 fewer cesarean deliveries, and 9.6 fewer maternal deaths in our theoretic cohort as compared to admission during latent labor. Additionally, delaying admission results in a cost savings of $694 million annually in the United States. Sensitivity analyses indicated the model was robust within a wide range of probabilities and costs. Monte Carlo simulation found that delayed admission was the optimal strategy in 76.79 percent of trials. CONCLUSION: Delaying admission until active labor is a dominant strategy, resulting in both better outcomes and lower costs. Issues related to clinical translation of these findings are explored.

Ting, A. Y., Xu, J., & Stouffer, R. L. (2015). Differential effects of estrogen and progesterone on development of primate secondary follicles in a steroid-depleted milieu in vitro. *Human Reproduction (Oxford, England)*,

STUDY QUESTION: What are the direct effects of progesterone (P4) and estradiol (E2) on the development and function of primate follicles in vitro from the pre-antral to early antral stage? SUMMARY ANSWER: In a steroid-depleted milieu, E2 improved follicle survival, growth, antrum formation and oocyte health, whereas P4 exerted minimal beneficial effects on follicle survival and reduced oocyte health. WHAT IS KNOWN ALREADY: Effects of P4 and E2 on follicle development have been studied primarily in large antral and pre-ovulatory follicles. Chronic P4 exposure suppresses antral follicle growth, but acute P4 exposure promotes oocyte maturation in

pre-ovulatory follicles. Effects of E2 can be stimulatory or inhibitory depending upon species, dose and duration of exposure. STUDY DESIGN, SIZE, DURATION: Non-human primate model, randomized, control versus treatment. Macaque (n = 6) secondary follicles (n = 24 per animal per treatment group) were cultured for 5 weeks. PARTICIPANTS/MATERIALS, SETTING, METHODS: Adult rhesus macaque secondary follicles were encapsulated in 0.25% alginate and cultured individually in media containing follicle stimulating hormone plus (i) vehicle, (ii) a steroid-synthesis inhibitor, trilostane (TRL, 250 ng/ml), (iii) TRL + low E2 (100 pg/ml) or progestin (P, 10 ng/ml R5020) and (iv) TRL + high E2 (1 ng/ml E2) or P (100 ng/ml R5020). Follicles reaching the antral stage (>/=750 microm) were treated with human chorionic gonadotrophin for 34 h. End-points included follicle survival, antrum formation, growth pattern, plus oocyte health and maturation status, as well as media concentrations of P4, E2 and anti-Mullerian hormone (AMH). MAIN RESULTS AND THE ROLE OF CHANCE: In a steroid-depleted milieu, low dose, but not high dose, P improved (P 0.05) on antrum formation and AMH production. Low-dose P increased (P < 0.05) P4 production in fast-grow follicles, and both doses of P elevated (P < 0.05) E2 production in slow-grow follicles. Additionally, low-dose P increased (P < 0.05) the percentage of no-grow follicles, and high-dose P promoted oocyte degeneration. In contrast, E2, in a steroid-depleted milieu, improved (P < 0.05) follicle survival, growth, antrum formation and oocyte health. E2 had no effect on P4 or E2 production. Follicles exposed to E2 yielded mature oocytes capable of fertilization and early cleavage, at a rate similar to untreated control follicles. LIMITATIONS, REASONS FOR CAUTION: This study is limited to in vitro effects of P and E2 during the interval from the secondary to small antral stage of macaque follicles. WIDER IMPLICATIONS OF THE FINDINGS: This study provides novel information on the direct actions of P4 and E2 on primate pre-antral follicle development. Combined with our previous report on the actions of androgens, our findings suggest that androgens appear to be a survival factor but hinder antral follicle differentiation, E2 appears to be a survival and growth factor at the pre-antral and early antral stage, whereas P4 may not be essential during early folliculogenesis in primates. STUDY FUNDING/COMPETING INTERESTS: NIH P50 HD071836 (NCTRI), NIH ORWH/NICHD 2K12HD043488 (BIRCWH), ONPRC 8P51OD011092. There are no conflicts of interest.

Turan, A., You, J., Egan, C., Fu, A., Khanna, A., Eshraghi, Y., et al. (2015). Chronic intermittent hypoxia is independently associated with reduced postoperative opioid consumption in bariatric patients suffering from sleep-disordered breathing. *Plos One*, *10*(5)
Background: Evidence suggests that recurrent nocturnal hypoxemia may affect pain response and/or the sensitivity to opioid analgesia. We tested the hypothesis that nocturnal hypoxemia, quantified by sleep time spent at an arterial saturation (SaO2)) 2 on polysomnography, are associated with decreased pain and reduced opioid consumption during the initial 72 postoperative hours in patients having laparoscopic bariatric surgery. Methods: With Institutional Review Board approval, we examined the records of all patients who underwent laparoscopic bariatric surgery between 2004 and 2010 and had an available nocturnal polysomnography study. We assessed the relationships between the time-weighted average of pain score and total opioid consumption during the initial 72 postoperative hours, and: (a) the percentage of total sleep time spent at SaO2 2, and (c) the number of apnea/hypopnea episodes per hour of sleep. We used multivariable regression models to adjust for both clinical and sleep-related confounders. Results: Two hundred eighteen patients were included in the analysis. Percentage of total sleep time spent at SaO2 2 2 was associated neither with total postoperative opioid consumption nor with pain. In addition, neither pain nor total opioid consumption was significantly associated with the number of apnea/hypopnea episodes per hour of sleep. Conclusions: Preoperative nocturnal intermittent hypoxia may enhance sensitivity to opioids. © 2015 Turan et al.

Turner, J. A., Comstock, B. A., Standaert, C., Heagerty, P. J., Jarvik, J. G., Deyo, R. A., et al. (2015). Can patient characteristics predict benefit from epidural corticosteroid injections for lumbar spinal stenosis symptoms? *The Spine Journal : Official Journal of the North American Spine Society*,
BACKGROUND CONTEXT: Epidural corticosteroid injections are commonly used to treat back and leg pain associated with lumbar spinal stenosis. However, little is known about which patient characteristics may predict favorable responses. PURPOSE: To identify patient characteristics associated with benefits from epidural injections of corticosteroid with lidocaine versus epidural injections of lidocaine only for lumbar spinal stenosis symptoms. STUDY DESIGN: Secondary analysis of LESS randomized controlled trial data. SETTING: 16 US clinical sites. PATIENT

SAMPLE: Patients > 50 years with moderate-to-severe leg pain and lumbar central spinal stenosis randomized to epidural injections of corticosteroids with lidocaine (n = 200) or lidocaine only (n = 200). OUTCOME MEASURES: Primary outcomes were the Roland-Morris Disability Questionnaire (RMDQ) and 0-10 leg pain intensity ratings. Secondary outcomes included the Brief Pain Inventory Interference Scale and the Swiss Spinal Stenosis Questionnaire. METHODS: At baseline, clinicians rated severity of patient spinal stenosis and patients completed predictor and outcome measures. Patients completed outcome measures again 3 and 6 (primary endpoint) weeks after randomization/initial injection. Analysis of covariance was used with treatment by covariate interactions to identify baseline predictors of greater benefit from corticosteroid + lidocaine versus lidocaine alone. We also identified nonspecific (independent of treatment) predictors of outcomes. The study was supported by Agency for Healthcare Research and Quality (AHRQ) grants 1R01HS019222-01 and 1R01HS022972-01, and Patient-Centered Outcomes Research Institute (PCORI) contract CE-12-11-4469. The authors report no study-related conflicts of interest. RESULTS: Among 21 candidate predictors and 6 outcomes, only one baseline variable predicted greater benefit from corticosteroid + lidocaine versus lidocaine only at 3 or 6 weeks. Compared to patients who rated their health-related quality of life as high on the EQ-5D Index, patients who rated it as poor had greater improvement with corticosteroid than with lidocaine only in leg pain at 6 (but not 3) weeks (interaction coefficient = 2.94; 95% CI = 0.11, 5.76; p = 0.04) and in RMDQ disability scores at 3 (but not 6) weeks (interaction coefficient = 4.77, 95% CI = -0.04, 9.59; p = 0.05). Several baseline patient characteristics predicted outcomes regardless of treatment assignment. CONCLUSIONS: Among 21 baseline patient characteristics examined, none, including clinician-rated spinal stenosis severity, were consistent predictors of benefit from epidural injections of lidocaine + corticosteroid versus lidocaine only.

Usher, C. (2015). Here/In this issue and There/Abstract thinking: Child psychiatry in the (mis)information age. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(7), 525-526.

van der Meulen, T., Donaldson, C. J., Caceres, E., Hunter, A. E., Cowing-Zitron, C., Pound, L. D., et al. (2015). Urocortin3 mediates somatostatin-dependent negative feedback control of insulin

secretion. *Nature Medicine*,

The peptide hormone urocortin3 (Ucn3) is abundantly expressed by mature beta cells, yet its physiological role is unknown. Here we demonstrate that Ucn3 is stored and co-released with insulin and potentiates glucose-stimulated somatostatin secretion via cognate receptors on delta cells. Further, we found that islets lacking endogenous Ucn3 have fewer delta cells, reduced somatostatin content, impaired somatostatin secretion, and exaggerated insulin release, and that these defects are rectified by treatment with synthetic Ucn3 in vitro. Our observations indicate that the paracrine actions of Ucn3 activate a negative feedback loop that promotes somatostatin release to ensure the timely reduction of insulin secretion upon normalization of plasma glucose. Moreover, Ucn3 is markedly depleted from beta cells in mouse and macaque models of diabetes and in human diabetic islets. This suggests that Ucn3 is a key contributor to stable glycemic control, whose reduction during diabetes aggravates glycemic volatility and contributes to the pathophysiology of this disease.

Verneris, M. R., Lee, S. J., Ahn, K. W., Wang, H. L., Battiwalla, M., Inamoto, Y., et al. (2015). HLA mismatch is associated with worse outcomes after unrelated donor reduced-intensity conditioning hematopoietic cell transplantation: An analysis from the center for international blood and marrow transplant research. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation*,

Over the past 2 decades, reduced-intensity conditioning allogeneic hematopoietic cell transplantation (RIC HCT) has increased substantially. Many patients do not have fully HLA-matched donors, and the impact of HLA mismatch on RIC HCT has not been examined in large cohorts. We analyzed 2588 recipients of 8/8 HLA-high resolution matched (n = 2025) or single-locus mismatched (n = 563) unrelated donor (URD) RIC HCT from 1999 to 2011. Overall survival (OS) was the primary outcome. Secondary endpoints included treatment-related mortality (TRM), relapse, disease-free survival (DFS), and acute/chronic graft-versus-host disease (GVHD). Adjusted 1- and 3-year OS was better in 8/8- versus 7/8-matched recipients (54.7% versus 48.8%, P = .01, and 37.4% versus 30.9%, P = .005, respectively). In multivariate models 7/8 URD RIC HCT recipients had more grades II to IV acute GVHD (RR = 1.29, P = .0034), higher TRM (RR = 1.52, P < .0001), and lower DFS (RR = 1.12, P = .0015) and OS (RR = 1.25, P =

.0001), with no difference in relapse or chronic GVHD. In subgroup analysis, inferior transplant outcomes were noted regardless of the HLA allele mismatched. Previously reported permissive mismatches at HLA-C (C*03:03/C*03:04) and HLA-DP1 (based on T cell-epitope matching) were not associated with better outcomes. Although feasible, single-locus mismatch in RIC URD HCT is associated with inferior outcomes.

Verweij, M. C., Horst, D., Griffin, B. D., Luteijn, R. D., Davison, A. J., Ressing, M. E., et al. (2015). Viral inhibition of the transporter associated with antigen processing (TAP): A striking example of functional convergent evolution. *PLoS Pathogens*, *11*(4)

Herpesviruses are large DNA viruses that are highly abundant within their host populations. Even in the presence of a healthy immune system, these viruses manage to cause lifelong infections. This persistence is partially mediated by the virus entering latency, a phase of infection characterized by limited viral protein expression. Moreover, herpesviruses have devoted a significant part of their coding capacity to immune evasion strategies. It is believed that the close coexistence of herpesviruses and their hosts has resulted in the evolution of viral proteins that specifically attack multiple arms of the host immune system. Cytotoxic T lymphocytes (CTLs) play an important role in antiviral immunity. CTLs recognize their target through viral peptides presented in the context of MHC molecules at the cell surface. Every herpesvirus studied to date encodes multiple immune evasion molecules that effectively interfere with specific steps of the MHC class I antigen presentation pathway. The transporter associated with antigen processing (TAP) plays a key role in the loading of viral peptides onto MHC class I molecules. This is reflected by the numerous ways herpesviruses have developed to block TAP function. In this review, we describe the characteristics and mechanisms of action of all known virus-encoded TAP inhibitors. Orthologs of these proteins encoded by related viruses are identified, and the conservation of TAP inhibition is discussed. A phylogenetic analysis of members of the family Herpesviridae is included to study the origin of these molecules. In addition, we discuss the characteristics of the first TAP inhibitor identified outside the herpesvirus family, namely, in cowpox virus. The strategies of TAP inhibition employed by viruses are very distinct and are likely to have been acquired independently during evolution. These findings and the recent discovery of

a non-herpesvirus TAP inhibitor represent a striking example of functional convergent evolution. © 2015 Verweij et al.

Vidhawan, S. A., Yap, A. U., Ornaghi, B. P., Banas, A., Banas, K., Neo, J. C., et al. (2015). Fatigue stipulation of bulk-fill composites: An in vitro appraisal. *Dental Materials : Official Publication of the Academy of Dental Materials*,

OBJECTIVES: The aim of this study was to determine the Weibull and slow crack growth (SCG) parameters of bulk-fill resin based composites. The strength degradation over time of the materials was also assessed by strength-probability-time (SPT) analysis. METHODS: Three bulk-fill [Tetric EvoCeram Bulk Fill (TBF); X-tra fil (XTR); Filtek Bulk-fill flowable (BFL)] and a conventional one [Filtek Z250 (Z250)] were studied. Seventy five disk-shaped specimens (12mm in diameter and 1mm thick) were prepared by inserting the uncured composites in a stainless steel split mold followed by photoactivation (1200mW/cm2/20s) and storage in distilled water (37 degrees C/24h). Degree of conversion was evaluated in five specimens by analysis of FT-IR spectra obtained in the mid-IR region. The SCG parameters n (stress corrosion susceptibility coefficient) and sigmaf0 (scaling parameter) were obtained by testing ten specimens in each of the five stress rates: 10-2, 10-1, 100, 101 and 102MPa/s using a piston-on-three-balls device. Weibull parameter m (Weibull modulus) and sigmaf0 (characteristic strength) were obtained by testing additional 20 specimens at 1MPa/s. Strength-probability-time (SPT) diagrams were constructed by merging SCG and Weibull parameters. RESULTS: BFL and TBF presented higher n values, respectively (40.1 and 25.5). Z250 showed the highest (157.02MPa) and TBF the lowest (110.90MPa) sigmaf0 value. Weibull analysis showed m (Weibull modulus) of 9.7, 8.6, 9.7 and 8.9 for TBF, BFL, XTR and Z250, respectively. SPT diagram for 5% probability of failure showed strength decrease of 18% for BFL, 25% for TBF, 32% for XTR and 36% for Z250, respectively, after 5 years as compared to 1 year. SIGNIFICANCE: The reliability and decadence of strength over time for bulk-fill resin composites studied are, at least, comparable to conventional composites. BFL shows the highest fatigue resistance under all simulations followed by TBF, while XTR was at par with Z250.

Viola, S., Traer, E., Huan, J., Hornick, N. I., Tyner, J. W., Agarwal, A., et al. (2015). Alterations in acute myeloid leukaemia bone marrow stromal cell exosome content coincide with gains in tyrosine kinase inhibitor resistance. *British Journal of Haematology*,

Wang, J., Sun, C., Gerdes, N., Liu, C., Liao, M., Liu, J., et al. (2015). Interleukin 18 function in atherosclerosis is mediated by the interleukin 18 receptor and the na-cl co-transporter. *Nature Medicine*,

Interleukin-18 (IL18) participates in atherogenesis through several putative mechanisms. Interruption of IL18 action reduces atherosclerosis in mice. Here, we show that absence of the IL18 receptor (IL18r) does not affect atherosclerosis in apolipoprotein E-deficient (Apoe-/-) mice, nor does it affect IL18 cell surface binding to or signaling in endothelial cells. As identified initially by co-immunoprecipitation with IL18, we found that IL18 interacts with the Na-Cl co-transporter (NCC; also known as SLC12A3), a 12-transmembrane-domain ion transporter protein preferentially expressed in the kidney. NCC is expressed in atherosclerotic lesions, where it colocalizes with IL18r. In Apoe-/- mice, combined deficiency of IL18r and NCC, but not single deficiency of either protein, protects mice from atherosclerosis. Peritoneal macrophages from Apoe-/- mice or from Apoe-/- mice lacking IL18r or NCC show IL18 binding and induction of cell signaling and cytokine and chemokine expression, but macrophages from Apoe-/- mice with combined deficiency of IL18r and NCC have a blunted response. An interaction between NCC and IL18r on macrophages was detected by co-immunoprecipitation. IL18 binds to the cell surface of NCC-transfected COS-7 cells, which do not express IL18r, and induces cell signaling and cytokine expression. This study identifies NCC as an IL18-binding protein that collaborates with IL18r in cell signaling, inflammatory molecule expression, and experimental atherogenesis.

Wang, M. L., Blum, K. A., Martin, P., Goy, A., Auer, R., Kahl, B. S., et al. (2015). Long-term follow-up of MCL patients treated with single-agent ibrutinib: Updated safety and efficacy results. *Blood*,

Ibrutinib, an oral inhibitor of Bruton tyrosine kinase, is approved for patients with mantle cell lymphoma (MCL) who have received one prior therapy. Herein, we report the updated safety and efficacy results from the multicenter, open-label phase 2 registration trial of ibrutinib (median 26.7-month follow-up). Patients (N=111) received oral ibrutinib 560 mg once daily, and those

with stable disease or better could enter a long-term extension study. The primary end point was overall response rate (ORR). The median patient age was 68 years (range, 40-84) with a median of 3 prior therapies (range, 1-5). The median treatment duration was 8.3 months; 46% of patients were treated for >12 months, and 22% were treated for >/=2 years. The ORR was 67% (23% complete response) with a median duration of response of 17.5 months. The 24-month PFS and OS rates were 31% (95% CI: 22.3-40.4) and 47% (95% CI: 37.1-56.9), respectively. The most common adverse events (AEs) in >30% of patients included diarrhea (54%), fatigue (50%), nausea (33%), and dyspnea (32%). The most frequent grade >/=3 infections included pneumonia (8%), urinary tract infection (4%), and cellulitis (3%). Grade >/=3 bleeding events in >/=2% of patients were hematuria (2%) and subdural hematoma (2%). Common all-grade hematologic AEs were thrombocytopenia (22%), neutropenia (19%), and anemia (18%). The prevalence of infection, diarrhea, and bleeding was highest for the first 6 months of therapy and less thereafter. With longer follow-up, ibrutinib continues to demonstrate durable responses and favorable safety in relapsed/refractory MCL. The trial is registered to www.ClinicalTrials.gov as NCT01236391.

Wang, N., Wang, C. -., Lian, X. -., Duan, S. -., Huang, D., & Zhou, S. -. (2015). Staging of development in Terrien's degeneration based on corneal curvatures detected by optical coherence tomography. *Graefe's Archive for Clinical and Experimental Ophthalmology*,

Purpose: We aimed to explore a new classification system based on the change of focal corneal curvatures and corneal thickness in Terrien's corneal degeneration with optical coherence tomography. Methods: This was a cross-sectional study. Ninety eyes of 59 patients with Terrien's degeneration were examined with slit lamp biomicroscopy, Orbscan II corneal tomography and the Visante OCT system, and were staged according to Süveges's classification. Results: The ratio of female to male patients was 1.57:1. The ratio of bilateral to unilateral lesions was 1.27:1. The occurrence of bilateral lesion was higher in males than in females ($x2 = 7.791$, $p = 0.005$). There was no difference in the mean age between female and male patients ($t = 1.859$, $p = 0.068$), or between patients with bilateral and unilateral lesions ($t = 1.797$, $p = 0.078$).The minimum corneal thickness at the thinnest point (MinCT) and anterior curvature of the peripheral cornea were almost normal in the initial stages of disease. The anterior curvature was flattened when

MinCT became less than 0.56 mm, returned to normal when MinCT was no more than 0.24 mm, and bowed forward when MinCT was no more than 0.13 mm. The posterior corneal curvatures were bowed forward from their normal curvatures in 42 of 90 eyes when MinCT was no more than 0.41 mm. These eyes' MinCT ranged from 0 to 0.41 mm. There was a strong correlation between change of corneal curvatures and MinCT (r = −0.943, p 1 vs. r2, −0.943 vs. -0.801). Conclusion: The proposed new classification based on focal corneal curvatures is closely associated with corneal thinning, is valuable for evaluating the development of Terrien's degeneration and may enhance surgical planning. © 2015 Springer-Verlag Berlin Heidelberg

Wang, P., Eshaq, R. S., Meshul, C. K., Moore, C., Hood, R. L., & Leidenheimer, N. J. (2015). Neuronal gamma-aminobutyric acid (GABA) type A receptors undergo cognate ligand chaperoning in the endoplasmic reticulum by endogenous GABA. *Frontiers in Cellular Neuroscience, 9*, 188.
GABAA receptors mediate fast inhibitory neurotransmission in the brain. Dysfunction of these receptors is associated with various psychiatric/neurological disorders and drugs targeting this receptor are widely used therapeutic agents. Both the efficacy and plasticity of GABAA receptor-mediated neurotransmission depends on the number of surface GABAA receptors. An understudied aspect of receptor cell surface expression is the post-translational regulation of receptor biogenesis within the endoplasmic reticulum (ER). We have previously shown that exogenous GABA can act as a ligand chaperone of recombinant GABAA receptors in the early secretory pathway leading us to now investigate whether endogenous GABA facilitates the biogenesis of GABAA receptors in primary cerebral cortical cultures. In immunofluorescence labeling experiments, we have determined that neurons expressing surface GABAA receptors contain both GABA and its degradative enzyme GABA transaminase (GABA-T). Treatment of neurons with GABA-T inhibitors, a treatment known to increase intracellular GABA levels, decreases the interaction of the receptor with the ER quality control protein calnexin, concomittantly increasing receptor forward-trafficking and plasma membrane insertion. The effect of GABA-T inhibition on the receptor/calnexin interaction is not due to the activation of surface GABAA or GABAB receptors. Consistent with our hypothesis that GABA acts as a cognate ligand chaperone in the ER, immunogold-labeling of rodent brain slices reveals the presence of GABA within the rough ER. The density of this labeling is similar to that present in mitochondria, the

organelle in which GABA is degraded. Lastly, the effect of GABA-T inhibition on the receptor/calnexin interaction was prevented by pretreatment with a GABA transporter inhibitor. Together, these data indicate that endogenous GABA acts in the rough ER as a cognate ligand chaperone to facilitate the biogenesis of neuronal GABAA receptors.

Wang, X., & Kroenke, C. D. (2015). Utilization of magnetic resonance imaging in research involving animal models of fetal alcohol spectrum disorders. *Alcohol Research: Current Reviews, 37*(1)
It is well recognized that fetal alcohol exposure can profoundly damage the developing brain. The term fetal alcohol spectrum disorder (FASD) describes the range of deficits that result from prenatal alcohol exposure. Over the past two decades, researchers have used magnetic resonance imaging (MRI) as a noninvasive technique to characterize anatomical, physiological, and metabolic changes in the human brain that are part of FASD. As using animal models can circumvent many of the complications inherent to human studies, researchers have established and explored a number of models involving a range of species. Using MRI-based modalities, the FASD animal models have demonstrated decreased brain volume and abnormal brain shape, disrupted cellular morphology differentiation, altered neurochemistry, and blood perfusion. These animal studies have facilitated characterization of the direct effects of ethanol; in many cases identifying specific sequelae related to the timing and dose of exposure. Further, as a result of the ability to perform traditional (such as histological) analyses on animal brains following neuroimaging experiments, this work leads to improvements in the accuracy of our interpretations of neuroimaging findings in human studies.

Whitmer, T., Malouli, D., Uebelhoer, L. S., DeFilippis, V. R., Fruh, K., & Verweij, M. C. (2015). The ORF61 protein encoded by simian varicella virus and varicella zoster virus inhibits NFkappaB signaling by interfering with IkappaBalpha degradation. *Journal of Virology*,
Varicella Zoster Virus (VZV) causes chickenpox upon primary infection and establishes latency in ganglia. Reactivation from latency causes herpes zoster, which may be complicated by post-herpetic neuralgia. Innate immunity mediated by interferon and pro-inflammatory cytokines represent the first line of immune defense upon infection and reactivation. VZV is known to

interfere with multiple innate immune signaling pathways including the central transcription factor NFkappaB. However the role of these inhibitory mechanisms in vivo is unknown. Simian varicella virus (SVV)-infection of rhesus macaques recapitulates key aspects of VZV pathogenesis and this model thus permits examining the role of immune evasion mechanisms in vivo. Here we compare SVV and VZV with respect to interference of NFkappaB activation. We demonstrate that both viruses prevent ubiquitination of the NFkappaB inhibitor IkBalpha, whereas SVV additionally prevents IkBalpha phosphorylation. We show that the ORF61 proteins of VZV and SVV are sufficient to prevent IkBalpha ubiquitination upon ectopic expression. We further demonstrate that SVV ORF61 interacts with beta-TrCP, a subunit of the SCF ubiquitin ligase complex that mediates the degradation of IkBalpha. This interaction seems to inactivate SCF-mediated protein degradation in general since the unrelated beta-TrCP-target Snail is also stabilized by ORF61. In addition to ORF61, SVV seems to encode additional inhibitors of the NFkappaB pathway since ORF61-deleted SVV still prevented IkBalpha phosphorylation and degradation. Taken together, our data demonstrate that SVV interferes with TNFalpha-induced NFkappaB activation at multiple levels which is consistent with the importance of these counter mechanisms for Varicella Virus infection. IMPORTANCE: The role of innate immunity during the establishment of primary infection, latency and reactivation by Varicella Zoster Virus (VZV) is incompletely understood. Since infection of rhesus macaques by Simian Varicella Virus (SVV) is being used as an animal model of VZV infection we characterized the molecular mechanism by which SVV interferes with innate immune activation. Specifically, we studied how SVV prevents activation of the transcription factor NFkappaB, a central factor in eliciting pro-inflammatory responses. The identification of molecular mechanisms that counteract innate immunity might ultimately lead to better vaccines and treatments of VZV since overcoming these mechanisms either by small molecule inhibition of by genetic modification of vaccine strains is expected to reduce the pathogenic potential of VZV. Moreover, using SVV-infection of rhesus macaques it will be possible to study increasing the vulnerability of varicella viruses to innate immunity will impact viral pathogenesis.

Wilhelm, C. J., Hashimoto, J. G., Roberts, M. L., Bloom, S. H., Andrew, M. R., & Wiren, K. M. (2015). Astrocyte dysfunction induced by alcohol in females but not males. *Brain Pathology (Zurich,*

Switzerland),

Chronic alcohol abuse is associated with brain damage in a sex-specific fashion, but the mechanisms involved are poorly described and remain controversial. Previous results have suggested that astrocyte gene expression is influenced by ethanol intoxication and during abstinence in vivo. Here, bioinformatic analysis of astrocyte-enriched ethanol-regulated genes in vivo revealed ubiquitin pathways as an ethanol target, but with sexually dimorphic cytokine signaling and changes associated with brain aging in females and not males. Consistent with this result, astrocyte activation was observed after exposure in female but not male animals, with reduced S100beta levels in the anterior cingulate cortex and increased GFAP+ cells in the hippocampus. In primary culture, the direct effects of chronic ethanol exposure followed by recovery on sex-specific astrocyte function were examined. Male astrocyte responses were consistent with astrocyte deactivation with reduced GFAP expression during ethanol exposure. In contrast, female astrocytes exhibited increased expression of Tnf, reduced expression of the neuroprotective cytokine Tgfb1, disrupted bioenergetics, and reduced excitatory amino acid uptake following exposure or recovery. These results indicate widespread astrocyte dysfunction in ethanol-exposed females and suggest a mechanism that may underlie increased vulnerability to ethanol-induced neurotoxicity in females.

Wilson, R. M., Marshall, N. E., Jeske, D. R., Purnell, J. Q., Thornburg, K., & Messaoudi, I. (2015). Maternal obesity alters immune cell frequencies and responses in umbilical cord blood samples. *Pediatric Allergy and Immunology*, *26*(4), 344-351.

Background: Maternal obesity is one of the several key factors thought to modulate neonatal immune system development. Data from murine studies demonstrate worse outcomes in models of infection, autoimmunity, and allergic sensitization in offspring of obese dams. In humans, children born to obese mothers are at increased risk for asthma. These findings suggest a dysregulation of immune function in the children of obese mothers; however, the underlying mechanisms remain poorly understood. The aim of this study was to examine the relationship between maternal body weight and the human neonatal immune system. Methods: Umbilical cord blood samples were collected from infants born to lean, overweight, and obese mothers. Frequency and function of major innate and adaptive immune cell populations were quantified

using flow cytometry and multiplex analysis of circulating factors. Results: Compared to babies born to lean mothers, babies of obese mothers had fewer eosinophils and CD4 T helper cells, reduced monocyte and dendritic cell responses to Toll-like receptor ligands, and increased plasma levels of IFN-α2 and IL-6 in cord blood. Conclusion: These results support the hypothesis that maternal obesity influences programming of the neonatal immune system, providing a potential link to increased incidence of chronic inflammatory diseases such as asthma and cardiovascular disease in the offspring.

Wingerchuk, D. M., Banwell, B., Bennett, J. L., Cabre, P., Carroll, W., Chitnis, T., et al. (2015). International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*,

Neuromyelitis optica (NMO) is an inflammatory CNS syndrome distinct from multiple sclerosis (MS) that is associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). Prior NMO diagnostic criteria required optic nerve and spinal cord involvement but more restricted or more extensive CNS involvement may occur. The International Panel for NMO Diagnosis (IPND) was convened to develop revised diagnostic criteria using systematic literature reviews and electronic surveys to facilitate consensus. The new nomenclature defines the unifying term NMO spectrum disorders (NMOSD), which is stratified further by serologic testing (NMOSD with or without AQP4-IgG). The core clinical characteristics required for patients with NMOSD with AQP4-IgG include clinical syndromes or MRI findings related to optic nerve, spinal cord, area postrema, other brainstem, diencephalic, or cerebral presentations. More stringent clinical criteria, with additional neuroimaging findings, are required for diagnosis of NMOSD without AQP4-IgG or when serologic testing is unavailable. The IPND also proposed validation strategies and achieved consensus on pediatric NMOSD diagnosis and the concepts of monophasic NMOSD and opticospinal MS.

Withycombe, B., Winden, J. C., Hassanyn, R., Duell, P. B., & Ito, M. K. (2015). The extent of familial hypercholesterolemia instruction in US schools and colleges of medicine, pharmacy, and osteopathic medicine. *Journal of Clinical Lipidology*, *9*(3), 281-288.

BACKGROUND: Familial hypercholesterolemia (FH) is a common autosomal codominant disease

characterized by extreme plasma cholesterol concentrations and high risk of early heart disease. FH is underdiagnosed and severely undertreated. This may be due in part to gaps in FH education within medical and pharmacy training programs. OBJECTIVES: To assess the extent to which FH is covered in professional curriculums in accredited schools and colleges of medicine, pharmacy, and osteopathic medicine in the United States. METHODS: An 18-question survey was distributed via e-mail to 288 US schools and colleges of medicine, pharmacy, and osteopathic medicine. RESULTS: Fifty-six of 288 (19.4%) programs responded to the survey. Three were excluded from analysis because of lack of program accreditation and FH instruction. Overall, 43% indicated that FH instruction at their respective institution was perceived to be adequate. More than 90% of the programs indicated that the following topics were covered within the curriculum: FH pathophysiology; associated morbidity and mortality; guideline-recommended low-density lipoprotein cholesterol goals and risk factor management; consequences of poor lipid management; and the screening, diagnosis, and treatment of adult patients. However, instruction was lacking for FH screening methods as one-third of the programs covered cascade screening and only half of the programs reported distinguishing between heterozygous and homozygous FH including differences in treatment approach. CONCLUSIONS: The results suggested important gaps in the coverage of FH in the curriculum, and strategies need to be developed to ensure that FH instruction is sufficient within these professional programs.

Wolfe, B. M., Blackburn, G. L., & Sanchez, V. M. (2014). *Surgical approaches and outcome in the treatment of the obese patients* Springer New York.

The surgical treatment of obesity is a consideration for individuals with severe obesity or obesity related comorbid conditions who have been unsuccessful in their effort to accomplish effective weight loss. Weight loss surgery is the most effective treatment for severe medical complicated and refractory obesity. Although there is a risk of postoperative complications, perioperative mortality is rare. It significantly ameliorates numerous life-threatening medical comorbidities that occur as part of the pathophysiology of obesity. Rapid changes in surgical technology and in demand for weight loss surgery have made the field one of medicines most dynamic. This chapter reviews available surgical procedures with possible mechanisms of action through the entero-

hypothalamic endocrine axis, and their risks and outcomes.

Wu, A. J., Bosch, W. R., Chang, D. T., Hong, T. S., Jabbour, S. K., Kleinberg, L. R., et al. (2015). Expert consensus contouring guidelines for intensity modulated radiation therapy in esophageal and gastroesophageal junction cancer. *International Journal of Radiation Oncology, Biology, Physics, 92*(4), 911-920.

PURPOSE/OBJECTIVE(S): Current guidelines for esophageal cancer contouring are derived from traditional 2-dimensional fields based on bony landmarks, and they do not provide sufficient anatomic detail to ensure consistent contouring for more conformal radiation therapy techniques such as intensity modulated radiation therapy (IMRT). Therefore, we convened an expert panel with the specific aim to derive contouring guidelines and generate an atlas for the clinical target volume (CTV) in esophageal or gastroesophageal junction (GEJ) cancer. METHODS AND MATERIALS: Eight expert academically based gastrointestinal radiation oncologists participated. Three sample cases were chosen: a GEJ cancer, a distal esophageal cancer, and a mid-upper esophageal cancer. Uniform computed tomographic (CT) simulation datasets and accompanying diagnostic positron emission tomographic/CT images were distributed to each expert, and the expert was instructed to generate gross tumor volume (GTV) and CTV contours for each case. All contours were aggregated and subjected to quantitative analysis to assess the degree of concordance between experts and to generate draft consensus contours. The panel then refined these contours to generate the contouring atlas. RESULTS: The kappa statistics indicated substantial agreement between panelists for each of the 3 test cases. A consensus CTV atlas was generated for the 3 test cases, each representing common anatomic presentations of esophageal cancer. The panel agreed on guidelines and principles to facilitate the generalizability of the atlas to individual cases. CONCLUSIONS: This expert panel successfully reached agreement on contouring guidelines for esophageal and GEJ IMRT and generated a reference CTV atlas. This atlas will serve as a reference for IMRT contours for clinical practice and prospective trial design. Subsequent patterns of failure analyses of clinical datasets using these guidelines may require modification in the future.

Xuan, C., Lun, L. M., Zhao, J. X., Wang, H. W., Wang, J., Ning, C. P., et al. (2015). L-citrulline for protection of endothelial function from ADMA-induced injury in porcine coronary artery. *Scientific Reports*, *5*, 10987.

Endogenous nitric oxide synthase (eNOS) inhibitor asymmetric dimethylarginine (ADMA) is a cardiovascular risk factor. We tested the hypothesis that L-citrulline may ameliorate the endothelial function altered by ADMA in porcine coronary artery (PCA). Myograph study for vasorelaxation, electrochemical measurement for NO, RT-PCR, and Western blot analysis for expression of eNOS, argininosuccinate synthetase (ASS), and p-eNOS(ser1177) were performed. cGMP was determined by enzyme immunoassay. Superoxide anion (O2.(-)) production was detected by the lucigenin-enhanced chemiluminescence method. Compare with controls (96.03% +/- 6.2%), the maximal relaxation induced by bradykinin was significantly attenuated (61.55% +/- 4.8%, $p < 0.01$), and significantly restored by L-citrulline (82.67 +/- 6.4%, $p < 0.05$) after 24 hours of ADMA exposure. Expression of eNOS, p-eNOS(ser1177), and ASS in PCA significantly increased after L-citrulline incubation. L-citrulline also markedly restored the NO production, and cGMP level which was reduced by ADMA. The increased O2.(-) production by ADMA was also inhibited by L-citrulline. L-citrulline restores the endothelial function in preparations treated with ADMA by preservation of NO production and suppression of O2.(-) generation. Preservation of NO is attributed to the upregulation of eNOS expression along with activation of p-eNOS(ser1177). L-citrulline improves endothelium-dependent vasodilation through NO/ cGMP pathway.

Xue, Y., Osborn, J., Panchal, A., & Mellies, J. L. (2015). The RpoE stress response pathway mediates reduction of the virulence of enteropathogenic escherichia coli by zinc. *Applied and Environmental Microbiology*, *81*(11), 3766-3774.

Zinc supplements are an effective clinical treatment for infantile diarrheal disease caused by enteric pathogens. Previous studies demonstrated that zinc acts on enteropathogenic Escherichia coli (EPEC) bacteria directly to suppress several virulence-related genes at a concentration that can be achieved by oral delivery of dietary zinc supplements. Our in vitro studies showed that a micromolar concentration of zinc induced the envelope stress response and suppressed virulence in EPEC, providing a possible mechanistic explanation for zinc's therapeutic action. In this report, we investigated the molecular and physiological changes in EPEC induced by zinc. We found that

micromolar concentrations of zinc reduced the bacterial growth rate without affecting viability. We observed increased membrane permeability caused by zinc. Zinc upregulated the RpoE-dependent envelope stress response pathway and suppressed EPEC virulence gene expression. RpoE alone was sufficient to inhibit virulence factor expression and to attenuate attaching and effacing lesion formation on human host cells. By mutational analysis we demonstrate that the DNA-binding motif of RpoE is necessary for suppression of the LEE1, but not the LEE4, operon. Predictably, inhibition of the RpoE-mediated envelope stress response in combination with micromolar concentrations of zinc reduced EPEC viability. In conclusion, zinc induces the RpoE and stress response pathways in EPEC, and the alternate sigma factor RpoE downregulates EPEC LEE and non-LEE virulence genes by multiple mechanisms.

Yackel, T. R. (2015). Capsule commentary on lee et al., patient use of email, facebook, and physicians' websites to communicate with physicians: A national online survey of retail pharmacy users. *Journal of General Internal Medicine*,

Yapundich, R., Applebee, A., Bethoux, F., Goldman, M. D., Hutton, G. J., Mass, M., et al. (2015). Evaluation of dalfampridine extended release 5 and 10 mg in multiple sclerosis: A randomized controlled trial. *International Journal of MS Care*, *17*(3), 138-145.
BACKGROUND: Dalfampridine extended-release (ER) tablets, 10 mg twice daily, have been shown to improve walking in people with multiple sclerosis. We evaluated the safety and efficacy of dalfampridine-ER 5 mg compared with 10 mg. METHODS: Patients were randomized to double-blind treatment with twice-daily dalfampridine-ER tablets, 5 mg (n = 144) or 10 mg (n = 143), or placebo (n = 143) for 4 weeks. Primary efficacy endpoint was change from baseline walking speed by the Timed 25-Foot Walk 3 to 4 hours after the last dose. At 40% of sites, 2-week change from baseline walking distance was measured by the 6-Minute Walk test. RESULTS: At 4 weeks, walking speed changes from baseline were 0.363, 0.423, and 0.478 ft/s (placebo, dalfampridine-ER 5 mg, and dalfampridine-ER 10 mg, respectively [P = NS]). Post hoc analysis of average changes between pretreatment and on-treatment showed that relative to placebo, only dalfampridine-ER 10 mg demonstrated a significant increase in walking speed (mean +/- SE):

0.443 +/- 0.042 ft/s versus 0.303 +/- 0.038 ft/s (P = .014). Improvement in 6-Minute Walk distance was significantly greater with dalfampridine-ER 10 mg (128.6 ft, P = .014) but not with 5 mg (76.8 ft, P = .308) relative to placebo (41.7 ft). Adverse events were consistent with previous studies. No seizures were reported. CONCLUSIONS: Dalfampridine-ER 5 and 10 mg twice daily did not demonstrate efficacy on the planned endpoint. Post hoc analyses demonstrated significant increases in walking speed relative to placebo with dalfampridine-ER 10 mg. No new safety signals were observed.

Yu, J., Jiang, C., Wang, X., Zhu, L., Gu, R., Xu, H., et al. (2015). Macular perfusion in healthy chinese: An optical coherence tomography angiogram study. *Investigative Ophthalmology & Visual Science, 56*(5), 3212-3217.

PURPOSE: To investigate macular perfusion in healthy Chinese individuals and examine its dependence on age and sex. METHODS: Healthy adult Chinese individuals were recruited. Macular perfusion was measured by spectral-domain optical coherence tomography (OCT) using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. The parafoveal flow index and vessel area density as well as the area of the foveal capillary-free zone (CFZ) were quantified. RESULTS: A total of 76 eyes in 45 subjects were included (20 males and 25 females, mean age 36 +/- 11 years). The mean parafoveal flow index was 0.099 +/- 0.013; the mean vessel area density was 0.891 +/- 0.073; and the mean CFZ area was 0.474 +/- 0.172 mm2. All three parameters were significantly correlated with age (flow index: P = 0.00; vessel area density: P = 0.00; CFZ area: P = 0.02). The flow index and vessel area density decreased annually by 0.6% and 0.4%, respectively, and CFZ area increased by 1.48% annually. The CFZ area was larger in females than in males, while all three parameters seemed to change more rapidly with age in males than in females. CONCLUSIONS: In healthy Chinese eyes, macular perfusion decreased with increasing age, and decreased more rapidly in males than in females. The application of OCT angiograms may provide a useful approach for monitoring macular perfusion, although caution must be exercised with regard to age- and sex-related variations.

Yu, L., Sawle, A. D., Wynn, J., Aspelund, G., Stolar, C. J., Arkovitz, M. S., et al. (2015). Increased burden of de novo predicted deleterious variants in complex congenital diaphragmatic hernia.

Human Molecular Genetics,

Congenital diaphragmatic hernia (CDH) is a serious birth defect that accounts for 8% of all major birth anomalies. Approximately 40% of cases occur in association with other anomalies. As sporadic complex CDH likely has a significant impact on reproductive fitness, we hypothesized that de novo variants would account for the etiology in a significant fraction of cases. We performed exome sequencing in 39 CDH trios and compared the frequency of de novo variants with 787 unaffected controls from the Simons Simplex Collection. We found no significant difference in overall frequency of de novo variants between cases and controls. However, among genes that are highly expressed during diaphragm development, there was a significant burden of likely gene disrupting (LGD) and predicted deleterious missense variants in cases (fold enrichment = 3.2, P-value = 0.003), and these genes are more likely to be haploinsufficient (P-value = 0.01) than the ones with benign missense or synonymous de novo variants in cases. After accounting for the frequency of de novo variants in the control population, we estimate that 15% of sporadic complex CDH patients are attributable to de novo LGD or deleterious missense variants. We identified several genes with predicted deleterious de novo variants that fall into common categories of genes related to transcription factors and cell migration that we believe are related to the pathogenesis of CDH. These data provide supportive evidence for novel genes in the pathogenesis of CDH associated with other anomalies and suggest that de novo variants play a significant role in complex CDH cases.

Zhang, Q. S., Deater, M., Schubert, K., Marquez-Loza, L., Pelz, C., Sinclair, D. A., et al. (2015). The Sirt1 activator SRT3025 expands hematopoietic stem and progenitor cells and improves hematopoiesis in fanconi anemia mice. *Stem Cell Research*, *15*(1), 130-140.

Fanconi anemia is a genetic bone marrow failure syndrome. The current treatment options are suboptimal and do not prevent the eventual onset of aplastic anemia requiring bone marrow transplantation. We previously showed that resveratrol, an antioxidant and an activator of the protein deacetylase Sirt1, enhanced hematopoiesis in Fancd2 mutant mice and improved the impaired stem cell quiescence observed in this disease. Given that Sirt1 is important for the function of hematopoietic stem cells, we hypothesized that Sirt1 activation may improve hematopoiesis. Indeed, Fancd2-/- mice and wild-type mice treated with the selective Sirt1

activator SRT3025 had increased numbers of hematopoietic stem and progenitor cells, platelets and white blood cells. SRT3025 was also protective against acetaldehyde-induced hematopoietic damage. Unlike resveratrol, however, SRT3025 did not affect stem cell quiescence, suggesting distinct mechanisms of action. Conditional deletion of Sirt1 in hematopoietic cells did not abrogate the beneficial effects of SRT3025, indicating that the drug did not act by directly stimulating Sirt1 in stem cells, but must be acting indirectly via extra-hematopoietic effects. RNA-Seq transcriptome analysis revealed the down-regulation of Egr1-p21 expression, providing a potential mechanism for improved hematopoiesis. Overall, our data indicate that SRT3025 or related compounds may be beneficial in Fanconi anemia and other bone marrow failure syndromes.

Zuloaga, D. G., Jacosbskind, J. S., & Raber, J. (2015). Methamphetamine and the hypothalamic-pituitary-adrenal axis. *Frontiers in Neuroscience, 9*, 178.

Psychostimulants such as methamphetamine (MA) induce significant alterations in the function of the hypothalamic-pituitary-adrenal (HPA) axis. These changes in HPA axis function are associated with altered stress-related behaviors and might contribute to addictive processes such as relapse. In this mini-review we discuss acute and chronic effects of MA (adult and developmental exposure) on the HPA axis, including effects on HPA axis associated genes/proteins, brain regions, and behaviors such as anxiety and depression. A better understanding of the mechanisms through which MA affects the HPA axis may lead to more effective treatment strategies for MA addiction.

Zuloaga, K. L., Zhang, W., Yeiser, L. A., Stewart, B., Kukino, A., Nie, X., et al. (2015). Neurobehavioral and imaging correlates of hippocampal atrophy in a mouse model of vascular cognitive impairment. *Translational Stroke Research,*

Vascular cognitive impairment (VCI) is the second most common cause of dementia. Reduced cerebral blood flow is thought to play a major role in the etiology of VCI. Therefore, chronic cerebral hypoperfusion has been used to model VCI in rodents. The goal of the current study was to determine the histopathological and neuroimaging substrates of neurocognitive impairments in a mouse model of chronic cerebral hypoperfusion induced by unilateral common carotid artery

occlusion (UCCAO). Mice were subjected to sham or right UCCAO (VCI) surgeries. Three months later, neurocognitive function was evaluated using the novel object recognition task, Morris water maze, and contextual and cued fear-conditioning tests. Next, cerebral perfusion was evaluated with dynamic susceptibility contrast magnetic resonance imaging (MRI) using an ultra-high field (11.75 T) animal MRI system. Finally, brain pathology was evaluated using histology and T2-weighted MRI. VCI, but not sham, mice had significantly reduced cerebral blood flow in the right vs. left cerebral cortex. VCI mice showed deficits in object recognition. T2-weighted MRI of VCI brains revealed enlargement of lateral ventricles, which corresponded to areas of hippocampal atrophy upon histological analysis. In conclusion, our data demonstrate that the UCCAO model of chronic hypoperfusion induces hippocampal atrophy and ventricular enlargement, resulting in neurocognitive deficits characteristic of VCI.